

MEDICAL NEUROBIOLOGY

PEGGY MASON

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MEDICAL NEUROBIOLOGY

PEGGY MASON, PHD

DEPARTMENT OF NEUROBIOLOGY
THE UNIVERSITY OF CHICAGO
CHICAGO, IL

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Over the years of this project, I often wondered why I chose to take on this task. In the end, I came to the realization that I wrote this book for the same reason that I teach neurobiology: to communicate the beauty, intricacy, and everyday importance of the nervous system.

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PREFACE

At the start of the 20th century, medical education in North America was almost universally substandard with few or no requirements for admission, graduation, or competency. In 1905, the American Medical Association boldly recommended broad changes including admission requirements, as well as an initial 2-year curriculum in basic science.¹ Over the ensuing decade, these recommendations were implemented in American and Canadian medical schools and have continued, with some modifications, to the current time. Currently, a full year of basic science by basic scientists is taught at most North American medical schools. A minority of the basic scientists who teach these courses have a medical degree, and an even smaller proportion are practicing clinicians. As a result, a tension has built up between the basic interests and abilities of the scientist teachers and the clinical interests and goals of the students desirous to be physicians. Basic scientists teach what is important to them more than what is clinically relevant, assuming that the medical students will receive clinical training in future courses on pathophysiology taught by clinicians. The medical students feel as though they are being asked to learn material that has varied relevance to their future profession. The fact that the goals of students and teachers differ hinders communication and frustrates both students and teachers. The innocent bystander hurt by this problem is the subject itself, the beautiful world of neurobiology.

I taught in the first-year medical neurobiology course at the University of Chicago for 15 years and directed this course for 7 years, encountering directly the tension between basic science and medicine. Throughout most of my participation in medical neurobiology, I taught what I considered fundamental neurobiological principles, along with the occasional clinical anecdote thrown in to pique the student's interest. A few years ago, however, I had the opportunity and pleasure of talking in depth with four medical students²—Markus Boos, Eileen Rhee, Vance Broach, and Jasmine Lew. The conversation occasioned an epiphany from which this book was born. My epiphany centered on (1) the volume of information that medical students must master in 2 years, from gross anatomy and histology to physiology, microbiology, and neurobiology; and (2) the impressive sincerity of medical students' desires to be great physicians and to help people.³ Understanding medical students'

¹ Council on Medical Education of the American Medical Association, JAMA 44:1470–75, 1905.

² At the time, all were students and now all are either residents or physicians.

³ It is my impression that the vast majority of medical students are motivated by some degree of altruism. In contrast, students pursue a Ph.D. degree in science for a number of reasons including the intellectual thrill, curiosity, the fun of laboratory work, and also in some, but certainly not all, cases the desire to improve human health. The often dichotomous motivations of basic scientists and physicians are another source of potential misunderstanding.

sincere altruism led to my recognition that any resistance that I perceived on the part of the students to learning course material was not attributable to disinterest or lack of motivation. Rather, students were making a realistic assessment of how to go from college-level biology to practicing medicine in 4 short years and were allotting their time and energy accordingly.

With my newfound insight, I looked anew at the material that we taught in medical neurobiology. I realized that a more comfortable union between basic science and clinical interests could and indeed *should* be forged. I now believe that what students deserve from a first-year, basic science neurobiology course is a logical framework that allows them to understand how the nervous system influences the breadth of human biology. An introductory course in neurobiology for medical students should *not* be designed to teach neurology. Rather, the goal should be to communicate the relevance of the nervous system to the practice of *every medical specialty* from cardiology to dermatology, neonatology, pediatrics, geriatrics, pulmonology, ophthalmology, and so on.

A single book in a single voice that teaches fundamental neurobiological concepts important to clinical practice was my objective in writing this textbook. Because this book is aimed more at the future internist than the future neurologist, no topic is covered in an encyclopedic fashion and thus this book is *not* a reference book. There are many outstanding reference books on topics related to the nervous system. Many of these were invaluable to me as I prepared this book. There are a number of excellent texts on neuroanatomy, neurology, and neuroscience that I encourage those of you whose interest is piqued to explore further.

Medical Neurobiology is intended to teach, explain, and clarify neurobiological concepts that *will* impact your lives as physicians. Essentially, your understanding is the ultimate test of the success of this book. Therefore, I am interested in your reactions, and I encourage you to send feedback to medneurobio@gmail.com.

No author is an island, and I certainly have benefited from the generosity and insight provided by countless individuals. In particular, I thank the hundreds of medical and graduate students whom I have taught over the years. Questions like “How do we sense wet?” have permitted me to see neurobiology afresh and also pushed me to learn new pieces of neurobiology. I feel particularly grateful to the Pritzker class of 2009 who, as my post-epiphany guinea pigs, worked with me to hone my ideas for how medical neurobiology should be taught. These students worked hard, they engaged the brain, struggled with the material, and most importantly, respected the brain—all that this basic scientist could ever ask for. My hope for this book is that it will catalyze more and more medical students to fully engage and appreciate the wonders of the nervous system.

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I thank Madelyn Baez, Thaddeus Brink, Howard Fields, Aaron Fox, Jay Goldberg, Elizabeth Grove, Kevin Hellman, Gert Holstege, Un Jung Kang, Don Katz, Philip Lloyd, Bob McCrea, Scott Mendelson, Kathy Millen, Malcolm Nason, Bob Perlman, Don Pfaff, Cliff Ragsdale, Peter Redgrave, Clif Saper, and Murray Sherman for their willingness to discuss and debate the mysteries of neural function and structure over the years. For generously and patiently responding to my questions, I am indebted to Ben Barres, Jack Feldman, Stanford Gregory, Jon Levine, Courtenay Norbury, Sam Sisodia, and Ruediger Thalmann. Cate Kiefe and Klara Scharnargl helped with illustrations. Jonathan Barnett, Andrew Bell, Adrian Danek, John Dowling, Andrew Engel, Patrick Hof, Anna Lysakowski, Jane Mason, Claude Perreault, Gisèle Perreault, and Caitlin Trasande were kind enough to share images with me, and I thank them. Larry Wood, Holly Humphrey, Scott Stern, and Halina Bruckner helped me find the common ground between basic science and medicine. Bob Burke, Lynette Daws, Elizabeth Grove, Kevin Hellman, Philip Lloyd, Bob Perlman, Peter Redgrave, Murray Sherman, Steve Shevell, Sarah Sweitzer, Tom Thach and Steve Waxman were kind enough to go over chapters, in some cases repeatedly. I am grateful to the University of Chicago and to my chairman, Murray Sherman, for support and encouragement throughout the years of this project.

A few people deserve special mention for help above and beyond either my expectations or my due. Philip Lloyd patiently read and commented on chapters on neural signaling over and over again, as well as on many additional chapters. His comments were always an entertaining blend of scientific rigor and wry humor. Philip saved me from numerous sloppy blunders, and I am more grateful than a forever supply of heirloom tomatoes can express. Bob Perlman has been an invaluable friend and source of encouragement. I have run to Bob repeatedly to understand the influence of evolution on our bodies and brains. Bob never disappoints. Bob possesses a unique blend of thoughtfulness, logical clarity, and compassion that I treasure. My friend and colleague, Kevin Hellman, has generously accompanied me on this journey, reading and commenting on *every chapter*. His humor, broad knowledge and interest in science, and positive attitude have buoyed my spirits time after time. Most importantly, the love for the brain implicit in Kevin's comments and suggestions has enriched this book immeasurably. Despite all of the help from my wonderful colleagues, mistakes remain. These mistakes are entirely due to my own shortcomings and stubbornness.

Craig Panner, my editor at Oxford University Press, believed in this project long before it was deserving of his faith. I remain both perplexed and deeply appreciative for his nearly immediate confidence in me and the project. Craig's calm served as the perfect antidote to this first-time author's occasional panic, and I am indebted to him for that. David D'Addona, also of Oxford University Press, was supportive, efficient,

and reassuring throughout this process, and I am thankful. Annie Woy saved me from many embarrassing slips of phrase.

My parents, Jane and Arthur Mason, have been a source of unfailing support and love all of my life. I am lucky to still rely on them in my advanced years. Over the years, my mother, a *Science News* devotee, has sent me hundreds of articles containing the word “brain.” Many of those articles have been valuable, and ideas from a few have found their way into this text. Even more valuable has been the faith and belief in me expressed by both of my parents in every possible way and on every possible occasion. My debt to them and love for them are infinite.

This book simply would not have been written without the support and love of Gisèle Perreault, my partner in love and life. Gisèle agreed to put our life together on hold in order for me to concentrate wholly on this book. She supported me emotionally when my energy flagged. Just as importantly, Gisèle challenged and pushed me in the honest way of a true partner. I would never have completed this project without her. I can never thank her enough.

*Peggy Mason
Chicago, IL*

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MEDICAL NEUROBIOLOGY

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SECTION I: INTRODUCTION

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CHAPTER 1

INTRODUCTION TO THE NERVOUS SYSTEM

THE SPINAL CORD, BRAINSTEM,
AND FOREBRAIN COMPRIZE THE
CENTRAL NERVOUS SYSTEM AND
EACH CONTRIBUTES DIFFERENTLY
TO NORMAL FUNCTION

At the age of 41, Jean-Dominique Bauby suffered a massive stroke that forced him from an exciting, glamorous Parisian life as the successful editor of the leading French fashion magazine *Elle* to a state of being “locked-in.” Like other patients with [locked-in syndrome](#), Bauby could not move his arms or legs nor could he speak, grimace, smile, sit, or hold up his head. He could not nod his assent nor signal his dissent. In short, he had no way to express himself to the outside world. Eventually, Bauby recovered enough to move his right eyelid. He coordinated with his nurse to spell out words by blinking out each letter. In this way, Bauby “dictated” a riveting account of his internal world, an account that was published as “The Diving Bell and the Butterfly” just days before Bauby died. In his memoir, Bauby describes his annoyance at the television being left on all night, the courtship of his ex-wife, and concerns about his friends’ long drive from Paris to visit him. Bauby’s experience while locked-in is remarkable for both the magnitude of what Bauby lost and the profound humanity that he retained. Bauby’s experience demonstrates, in dramatic fashion, the power of the human nervous system, the subject of this book.

As a result of his stroke, Bauby could no longer write, point, stand, or turn his eyes to look at his visitors. Bauby sensed parts of his body and face as numb, other parts as assaulted by pins and needles, and still other areas as the source of burning pain (see Box 1-1). Bauby was dependent on people and machines for nutrition, voiding, and breathing. Yet, he could still see and hear, although the latter function was limited to one ear. He followed normal rhythms, sleeping at night and staying awake during daylight hours. Most remarkably, Bauby’s inner life of thought and emotion was unimpaired: he remembered his past, considered his present fate, imagined his future, and described his life in heart-wrenching and poetic prose. In this introductory chapter, we consider in the most general terms how the functions that were compromised in Bauby—purposeful movement, sensory perception, homeostasis—and the abstract brain functions that Bauby retained are organized in the human brain.

Box 1-1

NERVOUS SYSTEM DAMAGE CAN MAKE NORMAL FUNCTIONS FAIL OR ABNORMAL SYMPTOMS APPEAR.

Damage to the nervous system gives rise to **negative signs** and to **positive signs**. Negative signs are clinical symptoms that result from the failure of a system to produce a function. Inabilities to move, feel, see, and hear are examples of negative signs. In contrast, positive signs are symptoms in which an abnormal symptom occurs in place of or in addition to normal functioning. Sensations of pins and needles or tingling are positive signs as are excess, unwanted movements or visual or auditory hallucinations. Bauby experienced both negative—the inability to move voluntarily—and positive—abnormal sensations of pins and needles and unprovoked pain—signs.

The nervous system contains two parts:

1. The **central nervous system**, comprised of those neurons that sit within the protective confines of the **dura** (see Box 1-2)
2. The **peripheral nervous system**, containing neurons with cell bodies outside of the dural envelope

The central nervous system has three major components, all of which are evident when we view the brain in the **sagittal plane** (see Box 1-3), meaning in profile. Figure 1-1 shows a mid-sagittal view, or sagittal slice through the midline, of the central nervous system which consists of:

1. The **spinal cord**, consisting of cervical, thoracic, lumbar and sacral regions
2. The **brainstem**, consisting of the **midbrain, pons, medulla**, and **cerebellum** (see Box 1-4)
3. The **forebrain**, consisting of the **cerebral cortex, basal ganglia**, and **thalamus**

Both the brainstem and the forebrain are contained within the skull and are commonly referred to as the **brain**. The spinal cord is also surrounded by bone, the vertebral column.

By considering a dramatic theatrical production as a metaphor for the nervous system, we can understand *roughly* the brain's organizational structure and division of labor:

- Actors are the interface with the audience: they act out the play and take in the audience's reaction. The spinal cord and brainstem provide our interface with the world, enabling us to move within the world and to

Box 1-2

PROTECTIVE LAYERS SURROUND THE NERVOUS SYSTEM.

The central nervous system (CNS) is surrounded by three specialized membranes, termed **meninges**. The integrity of these membranes is essential for the mechanical and chemical protection of the CNS. The outermost meningeal layer, the **dura mater** or simply **dura**, is a tough membrane that protects the CNS from penetration. The **arachnoid mater**, deep to the dura, forms a fluid-resistant sac around the brain and spinal cord. The innermost meninges, the **pia mater** is a very thin and delicate membrane separated from the arachnoid by the **subarachnoid space**, within which the brain's own fluid, **cerebrospinal fluid** or **CSF**, flows. The meninges surround the CNS but not the peripheral nervous system. Thus, the CNS transitions into the peripheral nervous system where the dura ends.

An analogous set of membranes to the meninges surrounds peripheral nerves. From the outside to the inside, these membranes are the **epineurium**, **perineurium**, and **endoneurium**, which act together to protect nerves from mechanical and chemical damage, as well as to ferry nutrients and waste between the nerves and blood. In some diseases, the protection afforded by the membranes surrounding peripheral nerves is compromised, leaving the nerves vulnerable to circulating substances. One example of this occurs in people with diabetes mellitus. Compromise of the membranes around nerves allows the high levels of circulating glucose present in some diabetic patients access to peripheral nerves. This access contributes to the pathogenesis of diabetic neuropathy, a common complication in diabetic patients with poorly controlled blood sugar.

Box 1-3

THERE ARE THREE ANATOMICAL PLANES OF SECTION.

There are three planes of section (see Fig. 1-1B):

Coronal

Horizontal

Sagittal

The coronal or **frontal** plane is parallel to the face (Fig. 1-1B). The horizontal plane is parallel to the top of the head, and the sagittal plane is the profile view, parallel to the side of the head. Since the human brain and spinal cord are at right angles relative to their orientation in quadrupeds, the coronal plane, commonly used to view the brain, is rarely used to view the spinal cord. In this book, all sections through the spinal cord are in the **transverse** plane, which cuts across the spinal cord (Fig. 1-1A).

sense the world. Just as actors may delay a line if the audience is laughing, the spinal cord and brainstem can provide rudimentary adjustments to movements when something unexpected occurs.

- The stage and house managers in a theater are analogous to the brainstem. The stage manager ensures that the actors have the appropriate props, lighting, and sound to act out the play, while the house manager guarantees that the theater is neither too hot nor too cold and so on. By analogy, the brainstem makes sure that the “actors” within the spinal cord and brainstem have the resources to perform as intended.
- The playwright, director, and producer together perform functions analogous to those of the forebrain. Based on personal experiences, the playwright details the lines and actions of each actor. In the forebrain, the cerebral cortex, the outer rind of the forebrain critical to cognitive function, processes events and surroundings and initiates purposeful movement, including verbal expression, based on experience. Each night, the director gauges audience reaction, decides whether to modify a line or change a scene on the following night, and communicates that decision to the actors. Similarly, the forebrain is able to learn from the past and adjust behavior for the future. The producer convinces backers to finance the play and decides who the target audience is and therefore, where and how to advertise the production. The forebrain provides us with the requisite skills to navigate among family members, friends, and strangers as the social animals that we are.

Of course, this analogy is not perfect and should not be extended too far or examined too closely. For example, not all sensory information comes into the nervous system through the spinal cord and brainstem (Fig. 1-2). The spinal cord receives sensory information from the body; the brainstem from the face, oral cavity, ears, and internal viscera; and the forebrain receives sensory information from the eyes and nose. The spinal cord and brainstem send signals out to control muscles and glands. The forebrain has no direct connection to muscles and can only reach the body through controlling the release of hormones from the **pituitary**, a major endocrine gland at the base of the brain. **Hypophysis**, Greek for *under-growth*, is an alternative name for the pituitary, which sits in a bony pocket underneath the base of the brain.

NORMAL SENSATION, MOVEMENT, AND HOMEOSTASIS DEPEND ON LONG-DISTANCE CONNECTIONS WITHIN THE CENTRAL NERVOUS SYSTEM

Buby's stroke nearly obliterated the middle portion of the brainstem (the pons), resulting in the loss of functions that depend on that part of the brainstem and, even more vitally, on functions that depend on a *connection*,

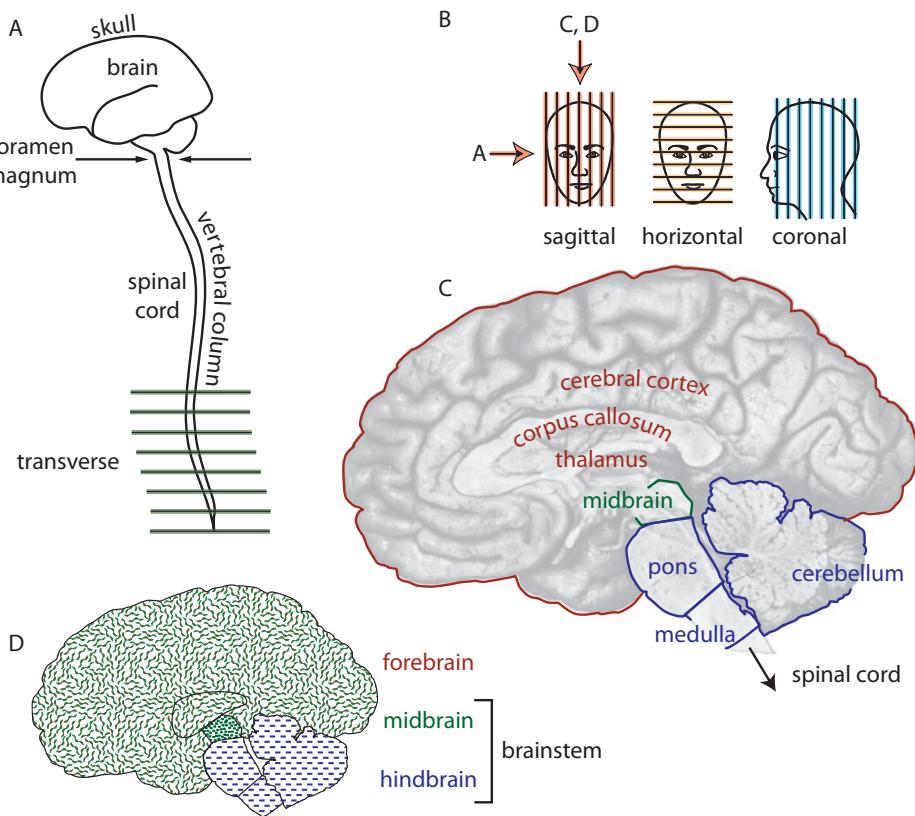


Figure 1-1. A: The central nervous system consists of the brain and the spinal cord, which are surrounded by the skull and the vertebral column, respectively. The foramen magnum is the large hole at the base of the skull where the brain and spinal cord meet. In this book, all sections through the spinal cord are transverse sections. B: Sagittal sections are taken as slices in the vertical plane going into the page, parallel to a Mohawk haircut. The sagittal section taken at the midline is termed the mid-sagittal section (arrow marked C, D). The diagram in A represents a view from the side (arrow marked A). Horizontal sections are slices parallel to the top of the head and coronal sections are parallel to the face. C: A mid-sagittal view of the human brain is shown with major parts of the hindbrain, midbrain and forebrain labeled. The visible parts of the forebrain are the cerebral cortex, corpus callosum, and thalamus. The midbrain has no subdivisions. The hindbrain consists of the medulla, pons, and cerebellum. D: The forebrain of the human brain dwarfs the midbrain and hindbrain in size. In fact, when viewed from the side, the midbrain is not visible, nor is most of the hindbrain. The cerebral cortex comprises the bulk of the forebrain. The relatively small thalamus is nestled deep within the forebrain and, like the midbrain, is not visible from the lateral surface of the brain.

Photograph in C reprinted with permission of deArmond S., et al. *Structure of the human brain: A photographic atlas*. New York: Oxford University Press, 1989.

Box 1-4

TWO DEVELOPMENTAL COMPARTMENTS MAKE UP THE BRAINSTEM.

The brainstem develops from two embryonic divisions: the embryonic midbrain, which becomes the adult midbrain, and the embryonic **hindbrain**, which develops into the medulla, pons, and cerebellum in the adult.

analogous to a street or highway, traveling through this region (Fig. 1-3). Bauby's grave condition resulted primarily from the latter: the stroke's disruption of connections. Bauby's stroke disconnected the forebrain and **rostral** brainstem from the **caudal** brainstem and spinal cord (Fig. 1-4). To understand how this disconnection could have had such profound effects, let us consider how the pathways that support sensation, movement, homeostasis, and higher brain functions traverse the spinal cord, brainstem, and forebrain and thus decipher how Bauby's brainstem stroke affects each function:

- Sensory information from the ears, oral cavity, skin, and viscera enters into the spinal cord and brainstem and then **ascends**, meaning that it travels from caudal to rostral, to the forebrain to give rise to auditory, gustatory, and somatosensory perception (see Box 1-5). Visual and olfactory information from the eyes and nose come directly into the forebrain. Since Bauby's stroke destroyed, nearly completely, the middle part of his brainstem while

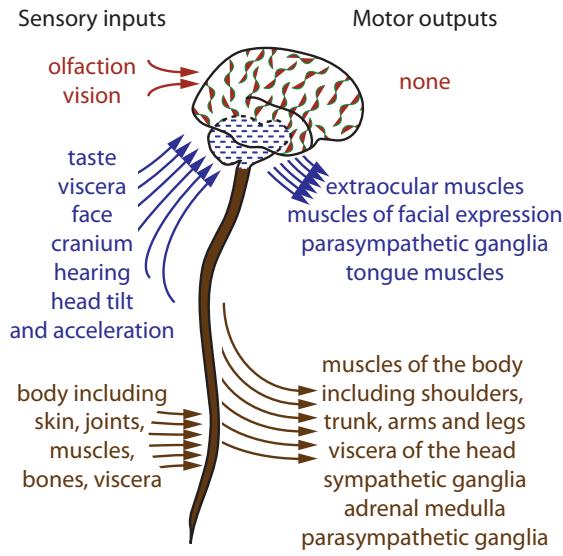


Figure 1-2. The spinal cord and brainstem mediate the bulk of the direct interactions with the world. Somatosensory inputs from the body enter the spinal cord and those from the face enter the brainstem. The brainstem also receives special sensory inputs from the inner ear and oral cavity, while olfactory and visual input enter directly into the forebrain. Output from the central nervous system arises solely from the brainstem and spinal cord. Motoneurons in the brainstem and spinal cord directly control all skeletal musculature. Smooth muscle, glands, and cardiac muscle are controlled indirectly, via peripherally located autonomic ganglia, by autonomic control neurons in the brainstem and spinal cord. The autonomic ganglia come in two varieties: parasympathetic and sympathetic, with the former controlled by neurons in the brainstem and sacral spinal cord and the latter controlled by neurons in the thoracic spinal cord. Bauby's lesion was in the pons and thus prevented him from receiving input from most ascending sensory pathways. The lesion also interrupted pathways from the forebrain to virtually all muscles and glands.

Figure 1-3. The central nervous system, from sacral (s) to lumbar (l) to thoracic (t) to cervical (c) cord to the brainstem, and then to the most rostral point of the forebrain, comprises the neuraxis. Sensory information ascends up the neuraxis and motor control information descends down the neuraxis. Sensory and motor pathways are involved in a variety of functions from the conscious control of skeletal muscles to the unconscious regulation of visceral function. The pathways involved in these varied functions involve both local and distant connections. For example, walking and chewing are motor activities that depend heavily on sensory input to and motor output from the spinal cord and hindbrain, respectively. The control of gaze depends on extensive connections between midbrain, hindbrain, and cervical spinal cord (not illustrated). Homeostatic functions, such as maintaining blood pressure when rising from a sitting position, depend on pathways between the brainstem and spinal autonomic motor neurons. Finally, the forebrain is unique in containing circuits that have only the most distant connections to sensory inputs and motor outputs. Such circuits, involved in abstract functions, were intact in Bauby, whose lesion covered much of the area within the orange bracket on the left.

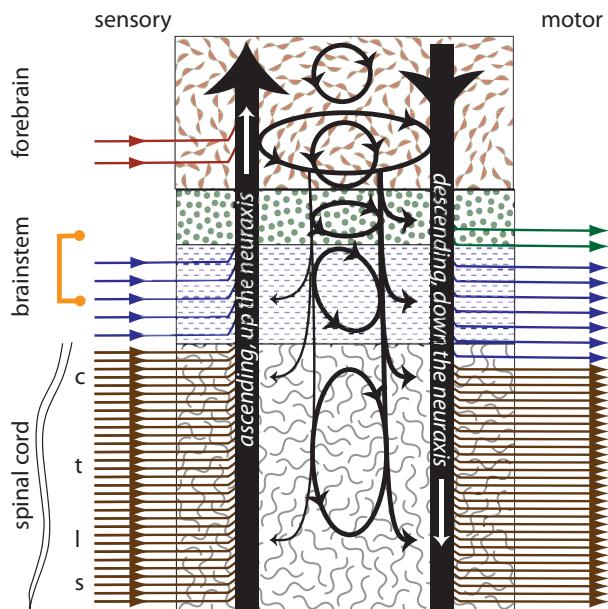
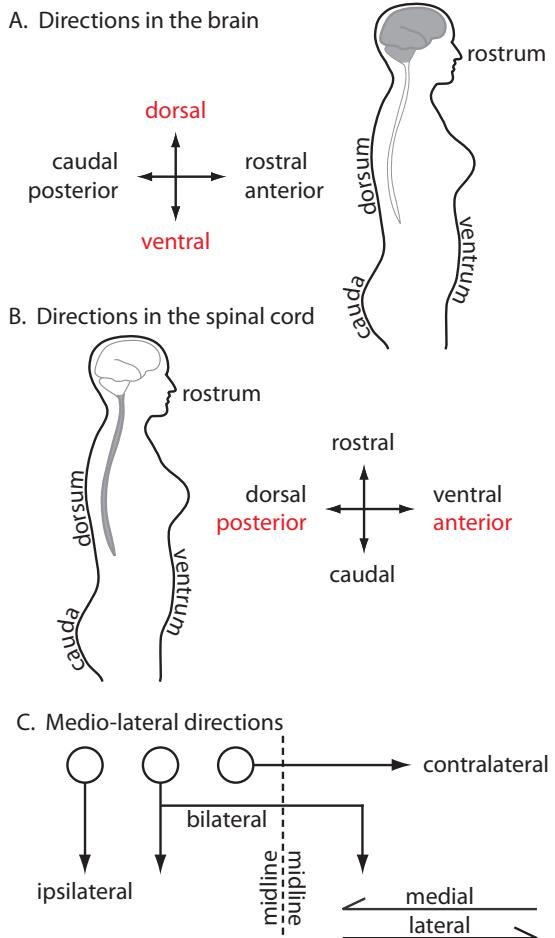


Figure 1-4. In the brain of the bipedal human (A), rostral, caudal, anterior and posterior have the same meaning as they do in a quadruped. Rostral, meaning toward the rostrum or nose, is synonymous with anterior, meaning in front. Caudal, meaning toward the cauda or tail (tail bone in our case), has the same meaning as posterior, meaning in back. Rostral and caudal are particularly helpful terms for locating structures along the length of the neuraxis, from the caudal tip of the spinal cord to the most rostral structures in the brain. We refer to the top of the brain as *dorsal*, or toward the dorsum or back, because in a quadruped the top of the brain is located dorsally. Similarly, the bottom of the brain is termed *ventral* because in a quadruped, it is located ventrally. In the spinal cord (B), rostral, caudal, dorsal, and ventral have the same meaning as they do in a quadruped. However, in the human spinal cord, anterior is synonymous with ventral and posterior with dorsal. **C:** Structures on the same side of midline are **ipsilateral**, whereas those on opposite sides of the midline are **contralateral**. Some neural pathways travel on both sides of midline, or **bilaterally**. **Medial** and **lateral** are terms that refer to toward and away from the midline, respectively.



Box 1-5

THE SOMATOSENSORY SYSTEM SUPPORTS A WIDE VARIETY OF CONSCIOUS AND UNCONSCIOUS SENSATIONS.

The **somatosensory system** carries information from skin, viscera, muscles, and joints that results in the perception of touch, pressure, vibration, pain, temperature, tickle, itch, wetness, and so on. The somatosensory system is also critical to a variety of unconscious functions, such as adjusting a grip, preventing stumbling, and maintaining blood pressure.

leaving his forebrain relatively intact, Bauby had impaired somatosensation, taste, and hearing (deaf in one ear) but could still see and smell.

- The neural origin of purposeful movement is in the cerebral cortex. **Cortical**, meaning of the cerebral cortex, projections *descend*, or travel from rostral to caudal, to reach motoneurons in the brainstem and spinal cord that in turn innervate skeletal or voluntary muscles (see Box 1-6). Bauby's stroke interrupted virtually this entire pathway, preventing him from moving at will. The only cortical projections to skeletal motoneurons remaining were from the cortex to the motoneurons controlling Bauby's eyelid.
- In order to maintain homeostasis, sensory information from the body enters the spinal cord and brainstem, where it triggers automatic or unconscious reactions. For example, in reaction to a mild decrease in ambient levels of oxygen, as occurs routinely in the passenger cabin of an airplane, we breathe more rapidly and elevate our blood pressure. Yet, we are not aware of this reaction, nor do we intentionally produce it. Sensory information ascends to the forebrain to engage more conscious adjustments, such as donning a windbreaker in response to cool sea breezes during a walk on the beach. Descending messages from the forebrain and brainstem reach

Box 1-6

WE HAVE VOLUNTARY CONTROL OVER MOST SKELETAL MUSCLES.

Skeletal muscle is striated muscle that is usually under voluntary control and typically attached to bones on either end. There are numerous exceptions to both of these rules. For example, swallowing muscles surrounding the esophagus are not attached to bone but to cartilage, and facial muscles attach to skin. An example of an involuntarily controlled skeletal muscle is the **stapedius**, located in the middle ear, which is controlled reflexively and serves to dampen sounds. Some skeletal muscles, such as the diaphragm, are voluntarily controlled, as when one sings an aria, or involuntarily controlled as when one breathes while asleep. In this book, the term *skeletal muscle*, imperfect though it may be, is used to refer to noncardiac striated muscle.

neurons that control muscles and glands to coordinate body functions with intended actions or particular circumstances. For example, as a frightened person runs from a growling dog, heart rate increases, digestion stops, and blood flow to the leg muscles increases. Although Bauby could feel the emotion of fear (because his forebrain was intact), he could not show that fear by any of the above manifestations because his stroke interrupted descending connections from his forebrain to brainstem and spinal circuits.

- Memory, attention, thought, emotion, and feelings toward others depend on forebrain neurons. The forebrain was not injured by Bauby's brainstem stroke and thus, these functions were intact.

MOTONEURONS ARE THE FINAL COMMON PATHWAY FOR EXPRESSION

The movement of **skeletal muscles** provides the only way that humans have to express themselves, whether explicitly through speech or writing or more implicitly through posture, facial expression, and eye movements. Since all purposeful human behavior consists of the actions of skeletal muscles, the ultimate outcome of movement is human nature itself. The only way to access the approximately 750 skeletal muscles of the body is via the roughly 100,000 **motoneurons** in the spinal cord and brainstem that send processes out to terminate on skeletal muscle cells. For this reason, Charles Sherrington called motoneurons the *final common pathway*, an unavoidable bottleneck that must be navigated to achieve willful expression (see Box 1-7).

Muscles cannot operate independently: *motoneurons that innervate skeletal muscles are absolutely necessary for motor function*. Muscles do not work without instructions from the central nervous system; they cannot even hold **tone** in the absence of neural input. Muscles that are unused and remain **flaccid**, or lax, for weeks and months eventually lose mass or **atrophy** (see Box 1-8).

Box 1-7

CHARLES SHERRINGTON WON THE 1932 NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE.

The Nobel prize was awarded for Sherrington's discoveries of how the nervous system integrates excitatory and inhibitory information to control basic movements or reflexes. Sherrington showed that sensory information from muscles, joints, and skin comes into the nervous system and engages

motor reflexes. Sherrington also demonstrated how **supraspinal** structures influence spinal motor reflexes. Sherrington is one of the most important figures in the history of neurophysiology, and our current understanding of neural circuits is rooted in Sherrington's fundamental findings.

MUSCLE TONE
REFERS TO THE
RESTING STATE OF
CONTRACTION IN A
MUSCLE.

Input from a motoneuron is necessary for muscle tone. Without motoneuron input, skeletal muscle loses tone, and becomes flaccid. An absence of motoneuron input can result from a traumatic injury that severs a nerve. More frequently, a disease process interferes with either the motoneuron directly or the communication between the motoneuron and the muscle. Diseases with this effect include **amyotrophic lateral sclerosis** and **myasthenia gravis**.

A MOTOR HIERARCHY CONTROLS THE ACTIVITY OF MOTONEURONS

The motoneuron is critical to movement but is not active in isolation. Therefore, motoneurons produce muscle contractions only when activated by inputs. When activated by other neurons, motoneuron activity leads to muscle contraction. Furthermore, when a motoneuron is activated in patterns dictated by neurons in the cerebral cortex, cerebellum, and basal ganglia, smooth motions involving multiple joints and muscles are produced. Since all central neurons influence motoneuron activity, directly or indirectly (in many cases, very indirectly), one can view the whole brain as “pre-motor,” functioning to control the activity of motoneurons. Yet, it is useful to concentrate on neurons that are most clearly related to the generation of movement; lesions in areas containing these neurons or their **axons**—long processes, or **fibers**, carrying neuronal output—produce disorders that dramatically affect voluntary movement with less dramatic effects on other functions, such as sensory perception and cognition. Such regions comprise a **motor hierarchy** that directs motoneuron activity, allowing for the full complement of movements that humans and other mammals produce.

REFLEXIVE MOVEMENT IS CONTROLLED BY THE LOWEST LEVEL OF THE MOTOR HIERARCHY

Movements must be adjusted to the external world, such as when an unexpected obstacle causes one to stumble. Incoming sensory input from skin, joints, and muscles provides information about where the body is in space and the muscles’ state of contraction or relaxation; such input is termed **proprioception**. Proprioceptive input is used as the starting point for adjusting movements to surprises such as a sudden drop in the terrain. In addition, potentially harmful inputs, such as heat from a flame or the prick of a thorn, elicit withdrawal movements that protect against further injury.

Most sensory input, as well as input from higher levels of the motor hierarchy, reaches motoneurons indirectly via neighboring neurons with local connections, neurons termed **interneurons**. The interneurons that influence motoneurons are integral to motor function and are called **motor interneurons**. When sensory input reaches motor interneurons and motoneurons, fundamentally automatic movements called **reflexes** occur. For example, proprioceptive inputs elicited by tripping over a child’s toy evoke a corrective stumbling reflex. Placing one’s hand on a hot stove excites nerves that signal pain and evoke a protective withdrawal reflex. Since there was nothing wrong with Bauby’s spinal cord, he still withdrew from a painful stimulus or jerked his leg in response to a tap on the knee.

CORTEX AND BRAINSTEM CONTAIN MOTOR CONTROL CENTERS CRITICAL TO VOLUNTARY MOVEMENT

Motor control centers in the cerebral cortex (see Box 1-9) produce movements through engaging descending pathways that ultimately result in the activation of motoneurons, which in turn produce muscle contraction. Cortical motor control regions are critical to fine movements of the digits, face, and mouth. When one dials a phone number, activity in neurons of primary motor cortex is translated into motoneuron activity that evokes the required movements in muscles of the arm, hand, and fingers (see Box 1-10). If the integrity of the motor control neurons or their paths to motoneurons are **lesioned**, meaning damaged, voluntary movement is no longer possible, an impairment that is termed **paralysis**.

The brainstem also contains motor control centers, ones critical for the maintenance of posture, orienting movements, and stereotypical movements such as chewing, swallowing, and locomotion. In Bauby's case, the brainstem, including its motor control centers and their connections, was largely destroyed, leaving Bauby unable to eat, drink, or walk on his own. Further, since the axons descending from virtually all motor control cells in the cortex were severed, Bauby had virtually no willful control of his muscles, save those in his right eyelid. As is the case in many individuals with locked-in syndrome, the motoneurons innervating the skeletal muscle of the eyelid were the least affected by Bauby's stroke. Eyelid motoneurons are often relatively spared in locked-in syndrome because they are located farthest away from the center of the area affected by the stroke. Furthermore, since damage from Bauby's stroke was more severe on the left side, it is understandable that eyelid motoneurons on the right were least affected.

THE CEREBELLUM LEARNS FROM PAST MOTOR EXPERIENCES TO ENSURE ACCURATE MOVEMENT EXECUTION

The cerebellum looks like a miniature version of the brain or **cerebrum**, and its name is a Latin diminutive of cerebrum. This mini-brain piggybacks on the back of the brainstem (Fig. 1-1C) and ensures that the movements we make are those that we intend to make. The cerebellum acts on movements involving several muscles and acting across several joints. One can think of the cerebellum as a conductor, not needed by the soloist or even a string quartet, but essential to the coordination of an orchestra. As an example of cerebellar function, when reaching out to shake someone's hand, our hand must travel toward the other person's hand, slow down just before reaching it, and then grasp the other's hand. Falling short of the outstretched hand or failing to slow upon nearing it will either make us appear

SPECIFIC BRAIN REGIONS ARE PREDOMINANTLY RESPONSIBLE FOR DISTINCT FUNCTIONS.

Within the five **lobes** of the cerebral cortex, function is modularly organized with different areas having predominantly separate functions. Most rostrally, the **frontal lobe** contains motor control centers, including **primary motor cortex**, as well as housing cortical areas critical to **executive function**, meaning decision-making (Fig. 1-5). A large invagination or **sulcus**, termed the **central sulcus**, separates the frontal lobe from the **parietal lobe** where **primary somatosensory cortex** sits. At the caudal end of the brain lies the **occipital lobe**, where vision is processed in **primary visual cortex**. Most of the primary visual cortex is located on the medial surface of the cerebral hemisphere, on either side of the **calcarine sulcus**. A large fissure, termed the **Sylvian fissure**, separates the **temporal lobe** from the overlying parietal and frontal lobes. The temporal lobe contains the **primary auditory cortex**. The temporal lobe contains a very important cortical region called the **hippocampus**. The hippocampus is essential for the formation of didactic memories. Bilateral damage to the hippocampi (plural of hippocampus) results in the inability to form new memories. Finally, deep within the recesses of the Sylvian fissure is the **insular lobe**, which serves many emotional and homeostatic functions.

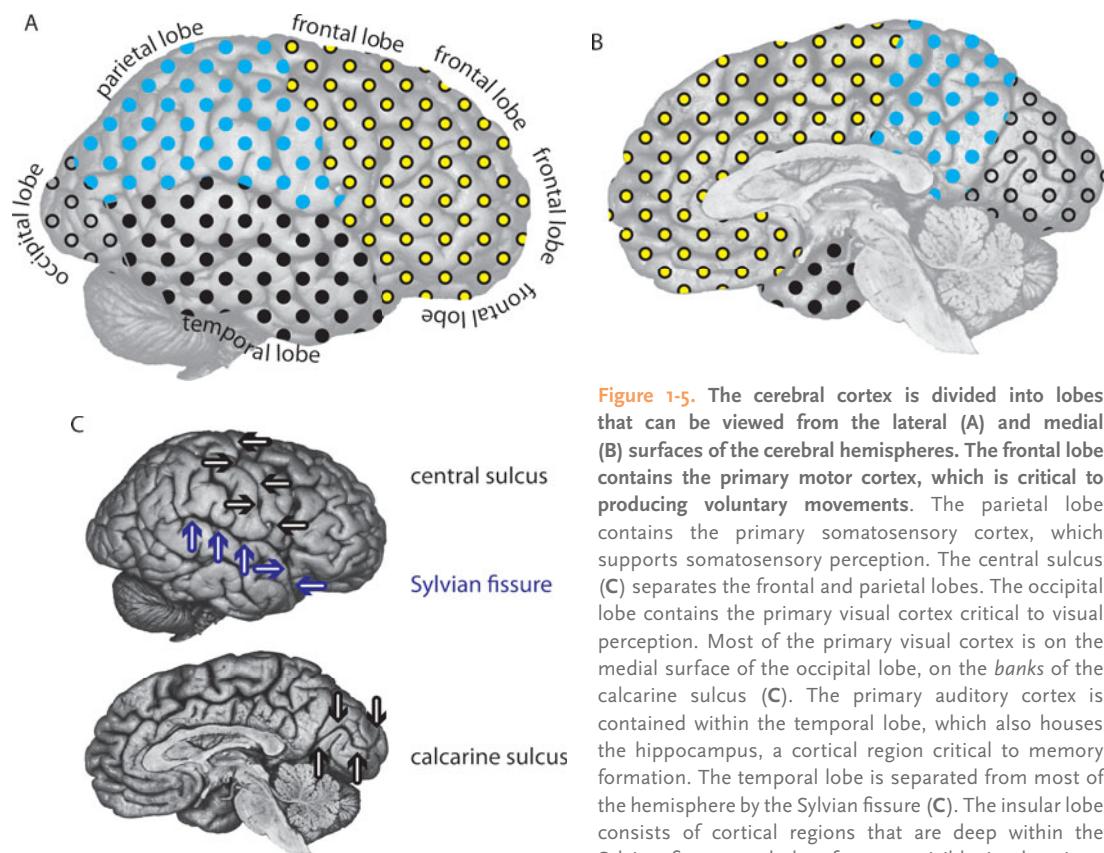


Figure 1-5. The cerebral cortex is divided into lobes that can be viewed from the lateral (A) and medial (B) surfaces of the cerebral hemispheres. The frontal lobe contains the primary motor cortex, which is critical to producing voluntary movements. The parietal lobe contains the primary somatosensory cortex, which supports somatosensory perception. The central sulcus (C) separates the frontal and parietal lobes. The occipital lobe contains the primary visual cortex critical to visual perception. Most of the primary visual cortex is on the medial surface of the occipital lobe, on the *banks* of the calcarine sulcus (C). The primary auditory cortex is contained within the temporal lobe, which also houses the hippocampus, a cortical region critical to memory formation. The temporal lobe is separated from most of the hemisphere by the Sylvian fissure (C). The insular lobe consists of cortical regions that are deep within the Sylvian fissure and therefore not visible in the views shown in A or B.

Photographs reprinted with permission of deArmond S., et al. *Structure of the human brain: A photographic atlas*. New York: Oxford University Press, 1989.

Box 1-10

CORTICAL NEURONS INDIRECTLY CONTROL MOVEMENT BY ACTIVATING BRAINSTEM AND SPINAL MOTONEURONS THAT CONTROL SKELETAL MUSCLES DIRECTLY.

Clinical literature often utilizes the term **upper motor neurons** to refer to cells in motor control centers, such as primary motor cortex, while referring to motoneurons that actually contact skeletal muscles as **lower motor neurons**. The idea behind this terminology—that motor control cells influence motoneurons so strongly that activity in the former *inevitably* leads to activity in the latter—is misleading. Motoneurons possess unique characteristics not shared by cells in motor control centers. Further, motoneurons directly contact muscle cells, also called *muscle fibers*, and control motor contraction absolutely, whereas motor control cells are only one of many sources of influence upon motoneurons. For these reasons, the terms upper and lower motor neurons are not employed in this book.

hesitant and unfriendly or worse yet, result in our hitting the other in the stomach. To prevent such inaccuracies, *the cerebellum learns what signals to send to which muscles to generate the forces necessary to achieve a designated action*. As babies, we cannot shake hands, not because we do not have the required muscles—we do—but because we have not yet trained our cerebellum to associate motor commands with the physical effects produced by those commands. After sufficient time playing and gesticulating, seemingly without purpose, children can make desired movements because their cerebellum has learned enough from past motor experiences to anticipate and prevent errors *before* they occur. Subsequent movements are “spot-on” or nearly so, even when performed for the first time.

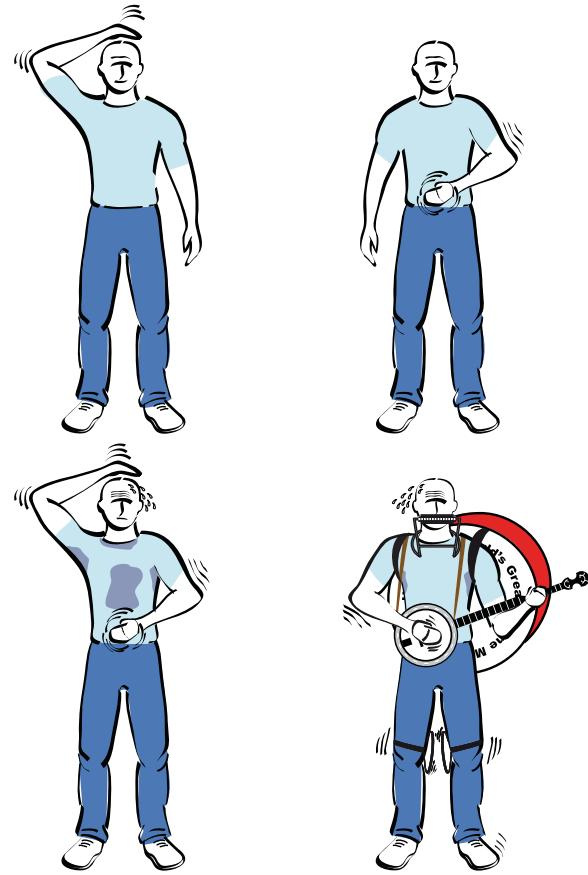
The cerebellum also functions to allow movements to proceed smoothly even when we encounter changed conditions while performing a familiar movement. As an example, when stepping from a boardwalk onto a sandy beach, we must walk with more force. The cerebellum adjusts gait and other movements to the ever-changing environment.

THE BASAL GANGLIA CHOOSE WHICH MOVEMENTS OCCUR

We all have only one set of muscles, and each muscle can do only one thing at a time. A person can only do one or a limited number of actions—chew gum and walk—at a single time. To appreciate this limitation, try to pat your head or rub your stomach. No problem, right? Now, try to pat your head and rub your stomach at the same time (Fig. 1-6). Although some people can do this after practice and with concentration, the fact that patting your head and rubbing your stomach at the same time requires *any* practice at all and *any* concentration demonstrates that our nervous system is not built for multiple simultaneous actions. Now try to pat your head and rub your stomach while also moving your foot back and forth and counting up by sevens. For the author, this group of actions is impossible; actually, I can hardly even achieve the first two actions simultaneously. Yet there is no good *physical* reason—e.g., falling over—why these actions cannot occur simultaneously, and each individual action is easy to accomplish when performed alone. The only obstacle to performing multiple actions simultaneously is *within the brain*. Apparently, the brain chooses to do one or a very few related actions while simultaneously suppressing all other movement. Within the human brain, the “chooser” is the basal ganglia. The basal ganglia are the ultimate arbiter, deciding which movement occurs and whether a movement continues or is interrupted by a more pressing action.

Just as the number of actions that we make at one time is limited, you can only have one perception at a time. In any of many visual illusions, a person switches between seeing two images but does not see both images at any one instant. For instance, in one popular illusion, one sees either a white vase or two silhouetted profiles facing each other, but not both images simultaneously (Fig. 1-7). As we explore in Chapter 25, just as the basal ganglia choose movements, they are also critical for “choosing” perceptions, thoughts, and emotions.

Figure 1-6. Everyone can pat their head (*upper left*) and everyone can rub their stomach (*upper right*). Yet, it takes effort to simultaneously perform two easy movements (*lower left*). Even more effort, practice, and sweat are needed to perform many simultaneous movements. A one-man band plays the banjo with his hands, the harmonica with his mouth, the cymbals with his knees, and the drum with his feet (*lower right*). With each additional movement, the effort and practice required are greater, and fewer people are able to successfully perform the motor multitasking.



PERCEPTION IS INTERPRETATIVE RATHER THAN FAITHFUL TO INTERNAL AND EXTERNAL STIMULI

Achieving a sensible representation of our world—external (how cold is it outside?) and internal (how well am I digesting lunch?)—is challenging. People who fail to recognize visual objects dramatically illustrate this challenge. The title character in Oliver Sacks' “The Man Who Mistook His Wife for a Hat,” Dr. P., describes an object that is handed to him as “about six inches in length, a convoluted red form with a linear green attachment,” but cannot name the object. His description of the rose clearly indicates a working visual system but Dr. P. cannot *interpret* what he sees, something that most of us do without thought or effort. Yet, upon smelling the mysterious object, Dr. P. instantly identifies it as “an early rose,” indicating that unlike Dr. P’s visual system, his olfactory system has access to stored knowledge and language production.

Making sense of our senses is challenging because interpretation is shaped by a myriad of factors. For example,



Figure 1-7. This image can be seen as a white vase or as the black profiles of two people facing each other. However, one cannot see both interpretations simultaneously.

the light bouncing off of a person viewed in sunshine or dim moonlight, sitting across a table or walking a block away, skipping rope or sleeping, is very different. Yet, regardless of appearing close or near, full face or in profile, above or below, illuminated by white or green light, a mother is still known by her child. The images in Figure 1-8 are all easily identified as a cat, although each image has a very different appearance. Put another way, the colors and contours of the five images differ markedly but all are interpreted as “cute cat.” Similarly, we can understand speech that is whispered, shouted, or sung in any number of accents and we recognize type in any number of fonts and sizes. There is no confusion in identifying a friend or relative, regardless of whether she talks, excited and bubbly, about her first day of work at a “dream job,” or dejectedly describes, in a soft low monotone, the car accident that she just had. Despite the very different timbre and pitch of the voices in the two situations, there is no confusion as to the speaker’s identity.

Although we are able to correctly identify a person in a variety of different lights, we also can discern the important differences between things that look remarkably similar. We eat a green apple but hit a tennis ball. We talk differently to an adult and a child or to a friend and a stranger. We write with a pencil but eat a breadstick. To make distinctions between similar objects we use both details of form—the apple is smooth and the tennis ball fuzzy—and context—the pencil is on the desk and the breadstick is on a table at a restaurant. Context and expectation also tell us that the knock came from a person behind the door and the bark from a dog, even when the dog, like the person, is on the other side of the door.

As sensory illusions show in dramatic fashion, perception is achieved by a liberal, context-specific interpretation of the world rather than by a faithful capture of external energy, such as that performed by cameras and tape recorders. There are examples

Figure 1-8. Three images are modified from the original photograph (top left). Although these images differ dramatically in optical attributes, all are easily interpreted as representing a cat.



where we sense things that are not actually there as well as instances when we fail to sense things that are there. If a mother says sternly to her child, “Come here right [cough] ow,” as she points to the ground in front of her, the child hears “Come here right now.” But if she says, “Look at the brown [cough] owl!” while pointing to cattle in a field, the child hears “Look at the brown cow.” The actual auditory information, cough-ow, that is alternately heard as “now” or “cow” is the same but is heard and interpreted differently, depending on the opening words and the situation or context. An example of the opposite phenomenon—not sensing a stimulus that is present in the world—happens to us every day as we fail to feel our clothes a short time after donning them.

HOMEOSTASIS IS THE PROCESS OF ENSURING THAT BODILY VARIABLES STAY WITHIN A PREFERRED RANGE

The human body operates best within certain physiological ranges, and these ranges are maintained by homeostatic functions that regulate internal body temperature, blood pressure, heart rate, electrolyte balance, body weight, sleep-wake cycles, and the like. Much of the physiological defense of the body occurs unconsciously through control of skeletal muscle, smooth muscle, cardiac muscle, and glands. The latter three targets are controlled in large part by the **sympathetic**, **parasympathetic**, and **enteric** divisions of the **autonomic nervous system**. Yet, voluntary behaviors also contribute to homeostasis. There is a continuum from functions that are completely unconscious to those with a large voluntary component:

- Many homeostatic functions occur without one’s ever being aware of their occurrence. For instance, every night, growth hormone is released during sleep. As another example, peristalsis pushes nutrients along within the intestines without our ever consciously contracting mesenteric smooth muscle.
- Other homeostatic functions are involuntarily controlled but impact on our awareness. An example of this is the vasodilation of cutaneous blood vessels that occurs as one heats up from exercise. A person can neither consciously dilate the skin’s vessels nor deliberately prevent cutaneous vasodilation from happening. “Oh, gee, I think I won’t sweat during my run today” is not an option. Instead, internal body heat triggers automatic reactions, including cutaneous vasodilation and sweating. Yet, unlike the case with the release of growth hormone, we are aware when heat-loss reactions happen.
- Much of our ability to maintain a stable core body temperature is achieved by voluntary actions such as wearing jackets in the winter, shorts and sandals in the summer, huddling in the cold, and jumping in the lake in the heat. Another example of a homeostatic function that requires voluntary movement is urination (**micturition** is the medical term for urination and will be used henceforth). In this case, the bladder muscle, a smooth muscle, is contracted automatically, but urine is not released unless the external urethral sphincter, a skeletal muscle, is willfully relaxed.

In sum, we maintain homeostasis using different combinations of behavioral or purposeful and autonomic or automatic actions.

HOMEOSTATIC CIRCUITS PREVENT OUT-OF-RANGE EXCURSIONS BEFORE THEY HAPPEN

Homeostasis is often modeled as a feedback system akin to a home's thermostat. However, a thermostat is "dumb" and only reacts to changes after they occur. In contrast, *the brain is "smart," and when possible, anticipates challenges to homeostasis*. For instance, saliva and insulin, a hormone released by the pancreas that regulates glucose metabolism, are released in anticipation of eating. Of course, there are also unexpected challenges to homeostasis, and these challenges are met by largely unconscious reflexes mediated by the spinal cord and/or brainstem. All anticipatory homeostatic adjustments require the forebrain, whereas many reflexive reactions do not.

Bauby had poor control over most homeostatic defense systems because his forebrain was cut off from his brainstem and spinal cord and because of extensive damage to his brainstem. He could not breathe or eat on his own and thus depended on a respirator and a gastric feeding tube. Even when Bauby knew he was going to be fed, his forebrain had no access to the neurons in the lower part of the brainstem that influence the pancreas, and thus he could not elicit insulin release in anticipation of feeding. As another example, every day, Bauby was strapped onto a board and nurses slowly raised him from a supine to a vertical position. This was accomplished very slowly to allow time for his spinal cord and lower brainstem to sense a drop in blood pressure and then reflexively raise his blood pressure. This function is normally performed quickly and unconsciously *prior* to intentionally "standing up," by a pathway from the forebrain, where the "decision" to stand up is initiated, to the spinal cord, where standing up is executed. Because his lower brainstem and spinal cord were intact, Bauby retained some homeostatic reflexive functions such as producing tears, salivating, and contracting his bladder when it was full. Yet, because his forebrain was disconnected from his brainstem and spinal cord, Bauby could not shed tears, swallow saliva, or release urine.

THE FOREBRAIN SUPPORTS HIGHER ABSTRACT BRAIN FUNCTIONS

Higher brain functions include language, attention, volition, emotion, memory, and the ability to socially interact with others. Our understanding of abstract brain functions relies on findings from psychology, psychiatry, and neurology as well as on basic neuroscience. For example, the lateralization of human language, to the left cortex in most individuals, was discovered by Paul Broca, a French clinician. Even now, most of our understanding of language

comes from human studies, although we are starting to benefit from the study of communication in nonhuman animals.

UNDERSTANDING BOTH REGIONAL AND FUNCTIONAL NEUROANATOMY IS CRITICAL TO CLINICAL PRACTICE

After a brief introduction (Section 1), we start by considering the electrical and chemical modes of neural communication (Section 2), and then move on to the anatomy of the nervous system (Section 3). Only after the basics of neurophysiology and neuroanatomy are understood do we begin to tackle how the brain “works” by examining perceptual (Section 4), motor (Section 5), and homeostatic (Section 6) functions. We end with a discussion of what understanding the nervous system can do for you in your chosen specialty (Section 7). As we shall see, the nervous system influences all human function and is thus relevant to understanding human behavior as well as to all clinical fields including dermatology, internal medicine, oncology, surgery, and so on.

The reader may wonder, “Why not concentrate entirely on material that is currently relevant to clinical practice?” There are two reasons:

- *Vocabulary:* If I started, for example, by presenting the pain system, I might tell you that the detection of a painful input requires the transduction, or conversion, of a noxious stimulus into graded potentials that trigger action potentials, which conduct down nociceptors to enter the dorsal horn via the dorsal roots. Nociceptors synapse in the dorsal horn onto spinothalamic neurons, which in turn decussate and project to the ventrobasal complex of the thalamus before eventually reaching the somatosensory cortex. However, if I started in this vein, we would have a serious communication problem, as only those previously exposed to neurobiology would understand. Instead, this book is designed for everyone interested in the medical basis and consequences of brain function, and it is my intention to not lose anyone by either assuming too much prior knowledge or by being too simplistic.
- *Clinical applications:* An additional reason to present regional neuroanatomy and basic cellular neurophysiology, as well as functional neural systems, is that neurological problems are sometimes regional. For example, a stroke in the brainstem, such as that which Bauby suffered, will incapacitate a region of the nervous system that contains neural elements involved in several functional pathways. Without an understanding of both regional anatomy and functional neural systems, there is no way to understand the presentation of different strokes and traumatic injuries.

To appreciate the need for understanding the brain from anatomical, cellular, and systems perspectives, consider a large metropolitan city as a metaphor for the nervous system. Just as is the case with the brain, the city is vulnerable to a myriad of disruptions. Let us first consider what would happen if a fire gutted a downtown high-rise. Residences and businesses in the building would be lost, while

those outside would carry on. On the day of the fire, people and cars would be blocked off from not only the affected building but also from the surrounding blocks. Utility lines running through the area would be interrupted, so that buildings neighboring the destroyed building, as well as the subway line traveling through the region, would be shut down. Recovery would slowly ensue. Within a day, people would be allowed to walk and drive through the region neighboring the destroyed building. After days to weeks, utility lines would be repaired, nearby buildings would be back to normal, and the subway line would run again. Overall, the city would be briefly disrupted but certainly not incapacitated by the fire. Such a major fire is a metaphor for traumatic injuries or **hemorrhagic strokes** that destroy brain tissue. As in the case of the metaphorical fire, brain injury destroys functions supported by the destroyed tissue (the residences and businesses in the building), and also increases travel time for neural pathways that run through or near the affected tissues. As in our metaphorical city, the brain will recover from injury, particularly in those regions surrounding the completely destroyed tissue. Unlike the metaphorical case, in which the high-rise can be rebuilt, destroyed brain tissue does not regenerate. As you may expect, the level of disruption is related to both the size of the area affected and the importance of the area destroyed: more disruption when a power plant is destroyed and less disruption when a park is leveled, more disruption when a quarter of the city is destroyed than when two blocks are destroyed. In the example that we have examined in this chapter, Bauby suffered a large stroke that hit a critical part of the brainstem, the rough equivalent of destroying most of downtown in a modern city.

Box 1-11

MYELIN INSULATES NEURONAL PROCESSES, ALLOWING FOR THE HIGHLY RAPID CONDUCTION OF ELECTRICAL SIGNALS ACROSS LONG DISTANCES.

Myelin is an insulation that wraps tightly around axons, the long processes of neurons, and enables the rapid transport of electrical signals across long distances. An axon that has a myelin wrap is a **myelinated** axon. Many things can go wrong with myelin. For example, the myelin wrapping can loosen, the immune system may attack and break down myelin, or a mutation may prevent production of a molecular component of myelin. When myelin is compromised for any reason, we term this **demyelination**. Impairment of neuronal communication results from demyelination (see Chapter 5).

Next, let us consider what happens when the power goes out in a large section of town. In this case, buildings are not destroyed, but there are a myriad of ramifications such as people being stuck in elevators, traffic lights going out and the ensuing car accidents, restaurants losing perishable goods, and theaters unable to go on with the show. If a chunk of brain loses power, as happens with an **ischemic stroke**, then the only way to be able to predict which functions will be affected is to know the regional anatomy of the brain. Just as the difficulty in getting the city powered back up depends on the area incapacitated, recovery from a loss of “power” in the brain does as well.

Third, consider a large accident that blocks the express lanes of the cross-town expressway. The city would not cease to function, and movement across the city would even continue. However, car movement across the city would be slowed, relegated to indirect routes through local streets. Similarly, disruption of the highways of the brain, termed **tracts**, occurs in **demyelinating** diseases such as **multiple sclerosis** (see Box 1-11). Demyelination does not block all communication between termini, but slows it down tremendously and causes lots of metaphorical traffic accidents. Depending on the city and the situation, a traffic disturbance will have different effects, perhaps delaying people’s trip to work, their return home, or their excursion to an evening concert. In the case of the brain, the only way to understand what effect disrupting a tract will have is to know the anatomy and connections of the brain and how these connections support function.

Finally, we consider what happens when there is a teacher’s strike in a major city. Children do not go to school, and education is severely compromised. However, many aspects of city life such as bars, restaurants, and clubs targeting

young single adults, professional sporting events, the city opera, and the like are unaffected by the teacher's strike. Likewise, there are viruses and diseases such as **herpes zoster**, **poliomyelitis**, **amyotrophic lateral sclerosis**, and **degenerative spinocerebellar ataxia** that target specific functional systems and not others. For this reason, we need to view the brain from the perspective of functional systems, such as vision or voluntary movement or respiratory control, and also to trace those parts of the brain that contribute to each such function.

In sum, this book is designed as a travel guide for the human brain. It is my hope to communicate to you the profound power and beauty of brain function while providing you with a memorable and enjoyable trip. Bon voyage!



ADDITIONAL READINGS

Bauby, J.-D. *The diving bell and the butterfly*. New York: Alfred A. Knopf, 1997.

Sacks, O. *The man who mistook his wife for a hat*. New York: Touchstone Books, 1985.

CHAPTER 2

CELLS OF THE NERVOUS SYSTEM: NEURONS AND GLIA

To understand the really fun parts of neurobiology, the reader must learn the meaning of hundreds of words, many of them anatomical. Overwhelmed students frequently ask whether learning the names of anatomical structures and details of anatomical pathways is *really* necessary. Here is an analogy to consider. At least 15–20 years after you learned your A-B-Cs, you now need to learn a new language, the language of the nervous system. Just as learning to recognize each letter when you were 5 years old may not have been a memorable or joyous occasion, you may not enjoy learning each neurobiological term. Nonetheless, to get to the good stuff—reading, in the case of the alphabet, and understanding human behavior, in the case of neurobiology—you must first assimilate the metaphorical A-B-Cs, and even the more rarely used Q-X-Zs.

As soon as you are able to recognize neuroanatomical sites, you can learn the neural functions of those sites, as well as some of the diseases and syndromes that affect them. However, just as you need to acquire a large vocabulary, rules of grammar, and some experience with children’s books in order to read and appreciate a piece of classic literature, you need a fairly detailed knowledge of neuroanatomy and neural signaling, and familiarity with some basic circuits before you can fully appreciate neural function. This book is designed to lead you on a journey from the most elemental neural building blocks to the most intriguing and sublime ways those building blocks work together in the human animal. Along the way, I hope to provide you with the tools to delve more deeply into whatever it is that intrigues you, and *surely every student will find something in the brain fascinating and worthy of further study.*

“FUNCTION” IS ONLY
AN APPROXIMATION OF WHAT
CELLS, BRAIN AREAS, AND
CIRCUITS ACTUALLY DO

As simple as it sounds, it is absolutely critical to appreciate that the nervous system works as a whole and within the context of the body. Throughout this book, we consider the function of discrete groups of cells when in fact *no part of the nervous system operates in isolation.* Consider the simplest neural

circuit: the **stretch reflex** (explored in Chapter 22). Even though the stretch reflex can be reduced to a minimum of two neurons and a muscle, it does not operate normally without thousands of other neuronal influences. The most commonly cited version of the stretch reflex—the knee jerk evoked by a tap below the kneecap—only requires one type of peripheral neuron, one type of neuron in the spinal cord, and the quadriceps muscle. Nonetheless, this same stretch reflex looks highly abnormal in someone with damage in the forebrain, a site far away from the location of the *necessary* neurons. The concept that a multitude of neurons in many regions influences multiple circuits and functions holds for *all* neural circuits, regardless of complexity. In sum, *while the component circuits in the nervous system can operate in isolation, they operate optimally within the integrated whole.*

Since the nervous system operates as an integrated whole, injury to one region will impact, perhaps minutely or perhaps hugely, many functions. Consider the analogy of identifying the function of your hands. Hand use is central to buttering bread, dealing cards, and washing your face. Although hands are absolutely necessary for all of these tasks, as well as many more, they are not dedicated to any of them. Therefore, it would be misleading to say that the function of hands is food preparation, entertainment, or hygiene. One could come nearer to the truth by characterizing the hands' function as one of manipulating objects. Yet, the hands function peripherally in myriad other tasks, such as gesticulating during speech or bearing weight when rising from a seated position. Although the words of a lecture or the final standing posture would be unchanged by loss of hand use, the information communicated by the lecture would be altered and the process of standing up would appear very different. In the case of the nervous system, *a single neural area or pathway may serve integrally in one or a few core functions but also contributes to countless other functions.*

Physiological function is an elusive concept, hard to decipher and harder to prove conclusively. To paraphrase the words of Niko Tinbergen, the great ethologist who shared the 1973 Nobel Prize in Physiology with Karl von Frisch and Konrad Lorenz, “We will never know whether a rooster crows because it is happy, or because it wants to wake the hens, or because it hates its neighbor” (Fig. 2-1). Similarly, we do not actually *know* the function of parts of the nervous system. The functions that I associate to anatomical regions or to molecules in the coming chapters represent best guesses in some cases and mnemonic approximations in others. Since the shorthand used below—such and such an area or such and such a receptor is critical to such and such a function—is inexact, *assignment of a function or functions to certain neurons or brain regions should not be viewed as a precise description of nervous system operation, but as a current best guess and as a teaching device.*

We now proceed, starting with identifying the cellular elements of the nervous system and describing the fundamental physiological and anatomical features of neurons.

NEURONS REQUIRE GLIA FOR SURVIVAL AND FUNCTION

Two essential cell types populate the nervous system: **neurons** and **glia**. Neurons are the credited actors of the nervous system, and beyond a few paragraphs here and there, are nearly the sole focus of this book. Yet, glial

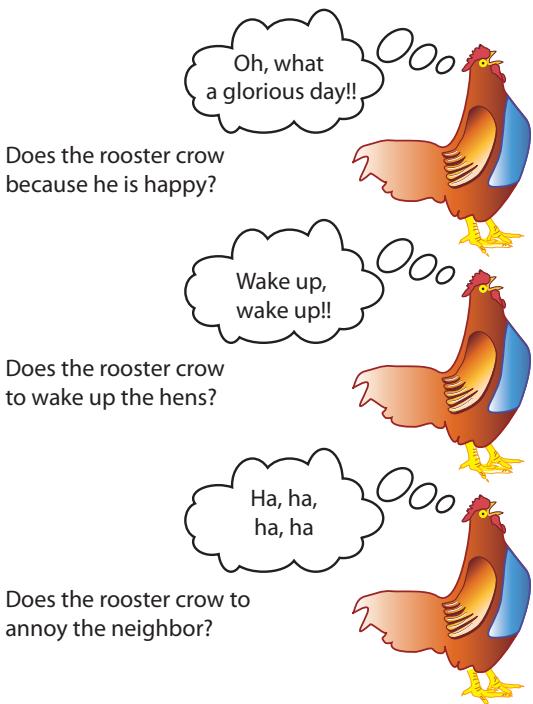


Figure 2-1. The function of the nervous system, like the intentions that drive behavior, can only be guessed at and approximated. Tinbergen summed this up beautifully in questioning the intentions behind a rooster's crowing.

Box 2-1

CELLS OF THE NERVOUS SYSTEM, WITH THE EXCEPTION OF MICROGLIA, DEVELOP FROM ECTODERMAL TISSUE.

Remember that the early embryo consists of three layers that, from inside to outside, are endoderm, mesoderm, and ectoderm. The endoderm develops into the viscera and digestive tract; the mesoderm into muscles, bones, and dermis; and the ectoderm forms the epidermis and the nervous system.

cells outnumber neurons by about 10 times. And just as the extras rather than the actors make a crowd scene, glia are critical to the development and patterning of the nervous system and provide necessary supportive services to adult neurons. Although the developmental, structural, environmental, and repair services of glia hold far less glory than do the lofty functions of neurons, neurons cannot survive and function without glia, just as a theatrical production would grind to a halt without the stage crew and production staff.

Small glia, termed **microglia**, resemble the peripheral immune cells known as macrophages. Microglia derive embryologically from mesodermal tissue as part of the hematopoietic lineage that gives rise to blood cells and thus are the only cells in the vertebrate nervous system that do not develop from **ectoderm** (see Box 2-1). The function, if any, of microglia under

healthy conditions is unclear. However, it is clear that microglia react to damage and disease. They sense substances indicative of damage or disease, including viruses, bacteria, and elevated extracellular levels of potassium ions, and respond by becoming **reactive** (see Box 2-2). Once in the reactive state, microglia promote inflammation and phagocytose damaged tissue and foreign matter. The beneficial or harmful nature of reactive microglia is currently controversial, and the possibility exists that reactive microglia both provide benefits and cause harm.

Large glial cells, termed **macroglia**, comprise 80%–90% of the body's glia. We recognize three main types of macroglia:

- **Schwann cells**
- **Oligodendrocytes**
- **Astrocytes**

Schwann cells and oligodendrocytes provide myelin, the insulating wrap around axons (see Box 1-11). By mechanisms that we explore in Chapter 5, myelin allows neuronal signals to travel rapidly and thus to traverse long distances in a short amount of time. Schwann cells provide myelin for axons in the periphery and oligodendrocytes for axons within the central nervous system (see Box 2-3).

Astrocytes are the workhorses of the glial family. They maintain ionic homeostasis in the extracellular fluid that surrounds neurons, playing a particularly important role in regulating potassium ion levels. Astrocytes rapidly clear some

Box 2-2

MICROGLIA APPEAR IMPORTANT IN THE BRAIN'S REACTION TO INJURY OR DISEASE.

Microglia become reactive in response to disease agents such as human immunodeficiency virus (HIV), the virus that causes acquired immune deficiency syndrome (AIDS); **prions**, the infectious agent that causes **Creutzfeldt-Jakob disease**; and **b-amyloid**, a protein that accumulates in the brains of patients with Alzheimer's disease. Reactive microglia are also found in the brains of patients with **Parkinson's disease** and in the spinal cord of animals with persistent pain. In all of the diseases mentioned above, reactive microglia contribute to an inflammatory process within the central nervous system. Although inflammation may be beneficial at early stages, it appears to be largely detrimental at later stages and is therefore the target of anti-inflammatory therapeutic efforts.

neurotransmitters, the nervous system's chemical communication agents, from **synapses**, the sites of communication between neurons, and thereby terminate many interneuronal dialogues. Astrocytes metabolize neurotransmitters and release the metabolites into the synaptic space, from where neurons can retrieve the metabolites to synthesize new neurotransmitter molecules. Beyond their importance to recycling certain neurotransmitters, astrocytes modulate the communication between neurons in important ways that are only recently beginning to be identified and understood. Finally, astrocytes contribute, sometimes in adverse ways, to many additional functions including the response to injury (see Box 2-4).

Glial cells are critical to the development of the nervous system. In one of the most often-cited examples of this importance, many newborn neurons migrate to their final destination along a scaffold composed of **radial glial cells**. Remarkably, after serving as neuronal scaffolds, some radial glial cells divide to give rise to neurons. Glial cells contribute to a number of additional developmental functions, including directing axons to their targets, promoting the survival of nascent neurons, and directing the formation of synapses.

NEURONS ARE DISTINCT CELLS THAT ANATOMICALLY INTERDIGITATE

In the 1830s, Schleiden and Schwann advanced the idea that the body was made up of small units called cells. **Cell doctrine** was applied to the whole body, except the central nervous system (CNS), where one large continuum or **syncytium** was postulated. However, in 1873, Camille Golgi developed a silver impregnation method, now known as the **Golgi stain**, which marks a tiny minority

Box 2-3

THE CENTRAL AND PERIPHERAL NERVOUS SYSTEMS ARE PROTECTED BY DISTINCT SETS OF MEMBRANES.

As introduced in Chapter 1, the central nervous system (CNS) is surrounded by three meningeal layers: the dura, arachnoid, and pia mater. The integrity of these membranes is essential for the mechanical and chemical protection of the CNS. *The meninges surround only the central nervous system and not the peripheral nervous system (PNS)*, and the converse is true as well: all of the CNS but none of the PNS is surrounded by meninges. Therefore the CNS transitions into the PNS at sites where the dura is absent.

Cells that have their cell bodies in the CNS are considered central neurons, even if they send their

axons into the periphery, as is the case for motoneurons (Fig. 2-2). Similarly, cells that bring sensory information from the periphery into the CNS, called **primary sensory afferents**, are considered peripheral neurons since they have a peripherally located soma. Sensory afferents are peripheral neurons even though they send an axon into the CNS. Different developmental paths for central and peripheral neurons render the categories of central and peripheral neurons biologically significant (see more on this in Chapter 3).

ASTROCYTES PROLIFERATE AT SITES OF INJURY, THEREBY PREVENTING REGROWTH.

Injury to the central nervous system (CNS) typically results in a proliferation of astrocytes termed **gliosis**. Newborn astrocytes assemble at the site of trauma or disease and form a **glial scar**. Axons lesioned by the trauma face great difficulty in navigating through the glial scar. The near impossibility of traversing glial scars in the CNS is a key reason why full recovery from physical damage to the CNS does not occur.

In striking contrast, peripheral axons can grow through the site of an injury. This difference has led to efforts to identify the molecules important in rendering the peripheral environment hospitable and the central environment inhospitable to the regrowth of axons. Eventually, the hope is that such knowledge will lead to the development of therapeutic agents that will enable regrowth centrally similar to that possible peripherally.

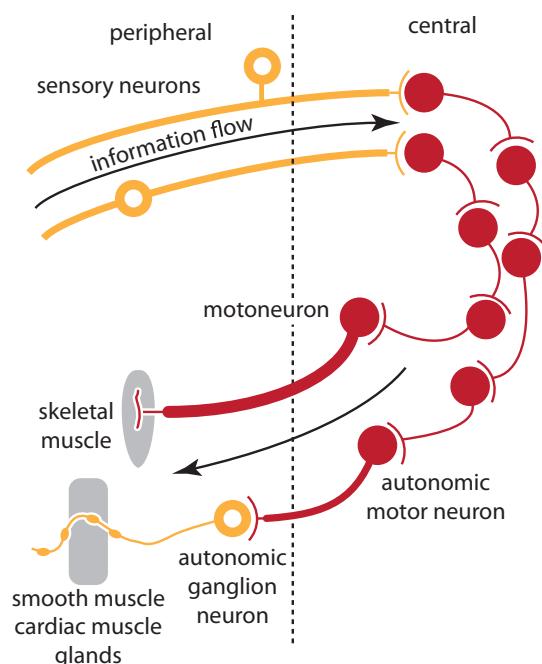


Figure 2-2. Central neurons are neurons with their cell body in the central nervous system and peripheral neurons (hollow) are neurons with their cell body in the peripheral nervous system. More than 99.99% of central neurons are contained entirely within the central nervous system, meaning that their soma, dendrites, and axon are located within the **confines of the meninges**. The only types of central neurons that send an axon into the periphery are motoneurons, which innervate skeletal muscle, and **autonomic motor neurons**, which innervate peripheral autonomic neurons. There are two major types of peripheral neurons, each residing in a **ganglion**, a globular mass of neurons. Sensory neurons have their cell body in a sensory ganglion, and autonomic neurons have their cell body in an autonomic ganglion. Autonomic ganglion neurons innervate smooth muscle, cardiac muscle, or glandular tissue. In the case of sensory neurons, one end of the neuronal process enters the central nervous system. In the case of autonomic neurons, the entire cell body and processes are located peripherally. Cells belonging to the enteric nervous system, not pictured here, are also peripheral neurons as they reside entirely within the walls of the digestive tract and therefore outside of the meninges. Sensory neurons, motoneurons, and autonomic ganglion neurons contain neuronal processes that are partly located centrally and partly peripherally. The myelinated axons of these neurons are myelinated by Schwann cells peripherally and by oligodendrocytes centrally. Note that dendrites are not illustrated to simplify the drawing.

of the cells in the CNS in their entirety—a great advancement over previously available stains. Using Golgi's staining technique, Ramon y Cajal, the greatest neuroanatomist of all time, and others, including Fridtjof Nansen of polar exploration fame, “saw,” or perhaps intuited, anatomical gaps between neuronal elements. Instead of a continuous, reticulated network, Cajal championed the **neuron doctrine**: *Each neuron is an entity unto itself which closely contacts but is not continuous with other neurons.* Cajal and Golgi shared the Nobel Prize for Physiology in 1906, although Golgi never subscribed to the neuron doctrine; indeed, Golgi used his Nobel Prize lecture to argue, incorrectly, that the brain is one continuous reticulated tissue.

THE MOST CONSISTENT NEURONAL TRAIT IS INDIVIDUALITY

There is no perfect definition of a neuron. Nonetheless, *most neurons share a group of traits that are not collectively shared by any other cell type.* Neuronal traits are listed in brief form here and explored in some detail below.

- All vertebrate neurons derive from ectoderm (see Box 2-1) and are postmitotic (see Box 2-5).
- Most neurons have three morphological regions beyond the cell body—the **dendrites**, an axon, and **synaptic terminals** (Fig. 2-3).
- Most neurons generate regenerative electrical potentials called **action potentials**, or colloquially put, most neurons *fire spikes*.
- Every neuron communicates with another neuron either on the input or output end or both (Fig. 2-2).

Neurons that depart from the typical neuronal profile include a variety of nonspiking neurons, including several cell types in the neural portion of the eye, the **neural retina**; and neurons that lack dendrites and/or an axon, such as many in

Box 2-5

MOST BRAIN TUMORS ARE NEOPLASMS OF GLIAL CELLS.

Most brain tumors are of glial rather than neuronal origin. The virtual absence of primary neuronal tumors may stem in part from neurons' being postmitotic. The most common type of primary (meaning that it starts locally) brain tumor is an **astrocytoma**, a neoplasm of astrocytes. The most severe grade of astrocytoma is **glioblastoma multiforme**, which typically results in death within a year or so of diagnosis. Another type of glioma, the **Schwannoma**, involves the proliferation of Schwann cells. The most common place for a Schwannoma to develop is at the root of the cranial nerve innervating the inner ear. These tumors are called **acoustic neuromas** and are relatively common and typically treatable. Neoplasms can also stem from an overproliferation of nonglial neuroepithelial cells. Examples of this include **meningiomas**, which contain cells of arachnoid origin, and pituitary adenomas, which contain pituitary cells.

Intracranial tumors are typically benign, meaning that they are unlikely to send metastases outside of the nervous system. Nonetheless, a benign brain tumor that cannot be surgically removed can be lethal if it continues to grow. The lethality of benign tumors stems from the limited space within the cranium and the deadly effects of elevated intracranial pressure (see much more on this topic in Chapter 14).

The brain is also vulnerable to metastases from malignant tumors of the lung, breast, kidney, and other tissues. Metastases can form at locations

throughout the brain, and the particular symptoms experienced are the result of the location. Metastatic masses within the cranium are common in part because of the high incidence of lung and breast malignancies. As with primary intracranial neoplasms, the first option for treatment is usually surgical.

An uncommon type of neurological disease stemming from a neoplasm is **paraneoplastic disease**. In paraneoplastic disease, a tumor, located outside the nervous system, releases a substance that negatively affects neural function or elicits an autoimmune reaction that in turn negatively affects neural function. An example of the former type of paraneoplastic disease is **Cushing's syndrome** resulting from the release of either adrenocorticotrophic hormone or a substance that mimics adrenocorticotrophic hormone (see Chapter 13). Patients with Cushing's syndrome typically have upper body obesity, excess hair growth, hypertension, and increased thirst and micturition reflective of impaired fluid homeostasis. Cushing's syndrome is most often secondary to small cell lung carcinoma. **Lambert-Eaton syndrome** is an example of an autoimmune paraneoplastic disease in which antibodies are formed in response to a tumor, typically a small-cell lung carcinoma (see Chapter 6). The antibodies impair synaptic transmission, and the most affected type of synapse is that between motoneurons and skeletal muscles. As a result, patients with Lambert-Eaton syndrome are weak.

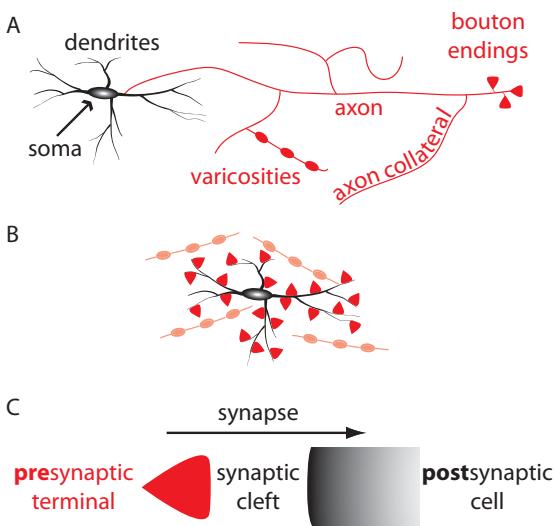


Figure 2-3. **A:** A typical neuron has a soma or cell body (black), and an axon with synaptic terminals (red). The daughter processes from a parent dendrite are called branches, whereas processes coming off of a parent axon are called collaterals. Axons and axon collaterals communicate via synaptic terminals in the form of either bouton endings or varicosities. The appearance of varicosities resembles slightly flattened pearls on a necklace, with the axon being the metaphorical necklace. Dendrites receive information and a neuron's axon carries information to target cells. **B:** Neurons receive an enormous number of synaptic inputs from bouton endings, varicosities, or both. **C:** At classical chemical synapses, a bouton ending and a dendrite are in close apposition, enabling communication from the **presynaptic** cell's bouton to the target, or **postsynaptic**, cell. The arrow shows the primary direction of information transfer across a synapse. Although the membranes of pre- and postsynaptic cells come very close to each other at classical synapses, they are separated by a narrow divide called the **synaptic cleft**. Note that these cartoons are not to scale but are drawn for illustrative purposes.

Box 2-6

THE MOST
CONSISTENT
NEURONAL
CHARACTERISTIC IS
INDIVIDUALITY.

As Herman Melville considered that “individual notabilities make up all totalities” in the world of whaling, a unique appearance, physiology, and function is the rule among neurons. Each neuron is unique or nearly so in its particular complement of neuronal properties.

the enteric nervous system. Conversely, astrocytes are close to neuronal doppelgängers as they derive from ectoderm, are mostly postmitotic and arguably communicate with neurons, although in ways that do not involve action potentials.

Perhaps the most important neuronal trait is individuality (see Box 2-6). In most organs of the body, there are a few, typically well under a dozen, different types of cells. This is true in the kidneys, lungs, and even in the relatively complex pancreas. However, in the nervous system, there are *thousands*, if not *millions*, of different types of neurons. Like stars in the sky that differ in location, age, color, and mass, one can argue that every neuron is different. Just as the Milky Way looks like a continuous mass rather than the aggregation of 200 billion individual and distinct stars, the brain appears as a continuous and cohesive tissue but is in fact comprised of hundreds of billions of individual cells. Neurons, like stars, differ from one another. In the case of neurons, individual differences in location, morphology, connections, physiological

characteristics, and ultimately function are myriad. Each neuron connects in unique ways to other cells, receiving a particular set of inputs and having a distinctive set of outputs. No two neurons in the mammalian nervous system are exactly alike, although cells within localized clusters, called **nuclei** (**nucleus** is the singular form), or layers, called **laminae** (**lamina** is the singular form), often share many common characteristics. Because the **connectivity** of a neuron provides the best clue as to the core functions of that neuron, the study of neuroanatomy is fundamental to neurobiology and occupies a section of this book.

INFORMATION FLOWS FROM THE SOMA AND DENDRITES TO THE AXON AND EVENTUALLY TO SYNAPTIC TERMINALS

Cajal made manifold contributions to neuroscience. Although he was a pure anatomist, looking at Golgi-stained sections day in and day out, Cajal's genius was that he saw function from structure, intuiting

process from the static picture afforded him by a light microscope of the late 19th and early 20th centuries. Cajal proposed that *neural information normally flows in one direction, from the dendrites and soma to the axon*. This idea, termed the **law of dynamic polarization**, now accepted dogma, suggests that after information travels down the axon, it then crosses over a physical divide to the dendrites and soma of another cell. This point of transfer, the place where two independent neuronal units communicate, was termed a *synapse* by Sir Charles Sherrington at the end of the 19th century. More important than popularizing the term synapse, Sherrington, the first great neurophysiologist and winner of the 1932 Nobel Prize in Physiology or Medicine (see Chapter 1), recognized the potential of the synapse to **integrate** excitatory and inhibitory information from multiple sources.

Box 2-7

PROGENITOR CELLS ARE CELLS THAT DIFFERENTIATE INTO SPECIFIC TYPES OF CELLS.

Progenitor cells are cells that are not fully differentiated and are still dividing. At each division, progenitor cells can give rise to two more progenitor cells—this is called **symmetric division**, or to a progenitor cell and a differentiated cell, termed **asymmetric division**. In the case of the nervous system, asymmetric division of progenitor cells gives rise to neurons or glial cells. One type of progenitor cell in the developing cerebral cortex is one and the same as the “radial glial cell.” Radial glial cells extend long processes along which newborn neurons migrate to reach their final positions. Thus, progenitor cells not only generate neurons but may also provide a migration scaffold for neurons to migrate along. Progenitor cells can also give rise to intermediate progenitor cells that divide to generate two neurons. At least two populations of neural progenitor cells have been identified in the adult brain.

ADDITIONAL CELL TYPES WORK WITH NEURONS AND GLIA IN PRODUCING NERVOUS FUNCTION

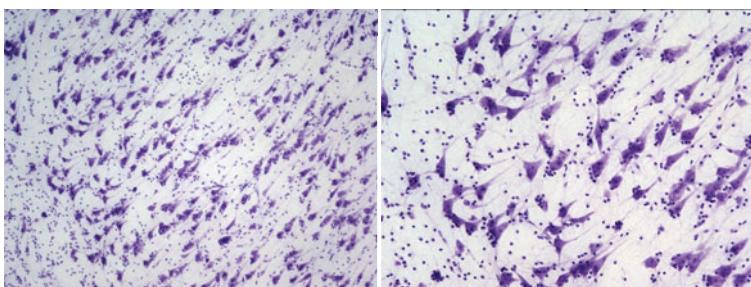
Beyond neurons and glia, several cell types hold honorary membership in the “neuro club.” Chief among these are muscle and glandular cells, which share many electrical signaling properties with neurons. In Section 5 on Motor Control, we will spend some time learning about different types of muscle fibers and how they produce force. A second type of neural companion cell is the epithelial sensory cell. Examples of non-neuronal sensory cells include the sensory receptor cells in the ear, both those involved in the sense of balance and those needed for hearing; and cells throughout the body that are sensitive to mechanical stimulation. A final cell type assisting neurons and glia is the **progenitor cell**, which is capable of producing neurons and glia (see Box 2-7).

NEURONAL COMPARTMENTS HAVE DIFFERENT ROLES

Each of the four anatomical subregions of the typical neuron—the soma, dendrites, axon, and synaptic terminal—has a primary role to play in neuronal function. As is true for all cells in the body, the soma houses the nucleus, the endoplasmic reticulum, Golgi apparatus, and other organelles that support cellular life. The rough endoplasmic reticulum in neurons is particularly active, synthesizing large quantities of proteins. Consequently, when stained with basophilic dyes, neuronal rough endoplasmic reticulum stands out prominently as **Nissl substance**. Staining brain sections for Nissl substance reveals the distribution of neuronal cell bodies and provides an easy and useful picture that can be used to readily identify gross changes or abnormalities in pathological specimens (Fig. 2-4).

Most synaptic terminals end on dendrites, and the dendritic tree is the primary receiving zone of the neuron, far more so than the soma. Some, but not all, neurons have dendrites with a multitude of small knob-like protuberances called

A. Nissl-stained section from hippocampus of normal control



B. Nissl-stained section from hippocampus of AD patient

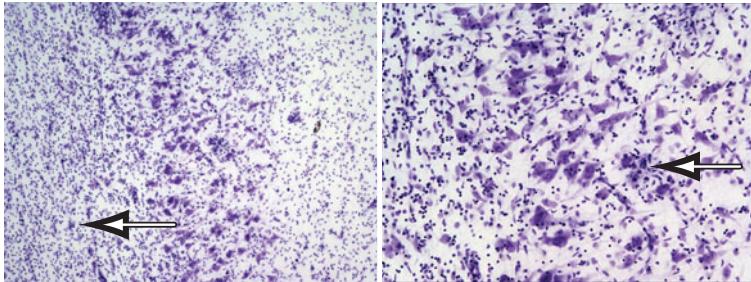


Figure 2-4. Nissl stains reveal somata but not neuronal processes. Nonetheless, these simple stains can reveal pathology and are commonly used by neuropathologists. In these photomicrographs of Nissl-stained sections through the hippocampus of a normal control (A) and a person with Alzheimer's disease (B), several differences are evident. The photomicrographs on the right are magnified images from the sections on the left. Neurons are reduced in number in the brain and packed more densely in the section from an Alzheimer's disease patient. In addition, marked gliosis (see Box 2-4) is evident from the plethora of tiny cells (arrow in left image of B). Finally, clumps of small cells, such as that indicated by the arrow in the right image of B, signal the presence of amyloid plaques, a pathological sign of Alzheimer's disease (see Box 14-9).

Photomicrographs kindly provided by Patrick R. Hof, Mount Sinai School of Medicine.

dendritic spines or simply spines. The head of the spine is globe-shaped and is linked to the main dendrite by a very thin process, the neck. Multiple inputs converge on spine heads, which form the subcellular locus of at least some, and perhaps most, changes associated with learning. Spines are thought to house anatomical changes central to storing memories.

Since all dendrites lead to the soma, synaptic input from the entire dendritic arbor reaches the soma. Within the soma, electrical signals derived from synaptic inputs are integrated. The axon arises from a point on or close to the soma, and it is at the start of the axon that synaptic inputs are “translated” into the language of action potentials that then travel down the axon to post-synaptic targets. Although neurons are typically only 5–25 microns in diameter, neuronal processes can be meters long, stretching from the foot to just inside the foramen magnum in short and tall people alike (see Box 2-8). As a result, the axon contains more than 99.9% of

the total neuronal volume. The fact that small neuronal somata, comprising no more than 0.1% of the neuronal volume, can support long processes, and do so for the decades of an individual's life, represents a tremendous biological achievement.

Box 2-8

THE DIMENSIONS OF SINGLE NEURONS VARY BY MANY ORDERS OF MAGNITUDE.

Most neuronal somata have an average somatic diameter of 5–25 microns¹ or so, whereas axonal diameter varies from less than a half micron up to 20 microns. In contrast, the longest neuronal processes stretch from the foot to the medulla, a distance of ≥ 1.4 meters in most adults. To put this

into perspective, if we represent a soma of 25 micron diameter by a baseball, then a thin process with a 1 micron diameter would be represented by a cylinder that is about the width of the thin end of a chopstick. The length of this “chopstick process” would be almost 3 miles long in a person of average height and over 3.5 miles in a tall individual. These staggering anatomical proportions highlight the biological challenges that neurons face in maintaining function throughout the extent of the entire cell.

¹ A micron, symbolized as μm , is 1/1000th of a millimeter; for those not familiar with the metric system, a millimeter corresponds to less than 0.04 inches. Thus, the largest neurons have a diameter of only a thousandth of an inch or so.

An important contributor to building and maintaining neurons in their vastness is a neuron-specific component of the cytoskeleton, the **neurofilament**, which is present throughout neurons, including within the soma and axon. In addition, because of their great length, neurons use methods for transporting substances from the soma to synaptic terminals and from synaptic terminals back to the soma. **Anterograde axonal transport** carries substances made in the soma, such as neurotransmitters or neurotransmitter-synthesizing enzymes (see Chapter 7), to synaptic terminals where these substances are used. **Retrograde axonal transport** carries substances from the synaptic terminals back to the soma. For example, synaptic terminals may pick up a trophic factor from a target cell and transport this factor back to the soma (see Box 2-9).

The raison d'être of an axon is to serve as a conduit, or transmission cable, for neural signals sent across a distance to reach the actual launching sites for neuronal communication, the synaptic terminals. The speed at which an axon supports **action potential conduction**, or travel, depends on the width of the axon and on whether the axon is wrapped in myelin. The axons with the fastest conduction times are large in diameter and heavily myelinated (see Box 2-10). Each axon has many synaptic terminals, from dozens to thousands, and the synapses in different areas look different. Regardless of the exact morphology adopted by the synapse, *the essence of synaptic communication is the transfer of information from a **presynaptic terminal** to a target or **postsynaptic** cell.*

Box 2-9

RETROGRADE AXONAL TRANSPORT IS USED BY NEURONS TO SIGNAL A HEALTHY CONNECTION TO THE TARGET CELL BUT CAN BE HIJACKED BY VIRUSES.

Trophic factors released from target cells can be picked up by synaptic terminals and then transported back to the soma via the axon. In the event of damage to either the axon or the synaptic terminal, retrograde transport is interrupted and trophic factors do not make it back to the soma. In this way, news of damage can reach the soma, which may be quite a distance away. For example, muscle fibers release factors that the terminals of motoneurons pick up. After damage to a nerve containing motoneuron axons, motoneurons undergo **chromatolysis**, a form of degeneration that can be detected using a Nissl stain. Chromatolysis is triggered by the absence of muscle-released factors transported back to the motoneuron soma.

The transport of trophic factors from the terminal to the soma provides neurons with continual

assurance that all is well. Unfortunately, this healthy process can be hijacked for nefarious purposes. Several **neurotropic** viruses are picked up at peripheral terminals and retrogradely transported to the parent somata. For example, **varicella zoster virus**, the causative agent of chickenpox, is picked up by the terminals of sensory neurons and transported back to the parent somata in a sensory ganglion. Zoster virus can remain in an inactive state in the sensory neuron somata for decades. In some individuals, the virus reactivates, causing an outbreak of **herpes zoster** (see Chapter 18). Another example of a neurotropic virus is the **poliovirus**, the causative agent of poliomyelitis. Poliovirus is picked up at the muscle by the terminals of motoneurons and ultimately can lead to the degeneration of infected motoneurons, resulting in a paralysis of the muscles involved.

Box 2-10

GRAY MATTER REFERS TO COLLECTIONS OF CELLS AND WHITE MATTER TO TRACTS OF MYELINATED AXONS.

Myelin is white. Consequently, areas with concentrations of myelinated axons have an overall white appearance. In contrast, areas with cells, dendrites, and unmyelinated axons appear gray in unstained brains. Thus, regions of cells are termed **gray matter**, and areas containing axonal tracts are termed **white matter** (Fig. 2-5). It should be remembered that various histological stains can alter the appearance of gray matter, white matter, or both. For example, application of myelin stains renders white matter blue or black and makes the unstained gray matter appear white. Indeed, some of the photomicrographs, particularly in Section 3, are of myelin-stained tissue in which “white matter” appears dark and “gray matter” appears light.

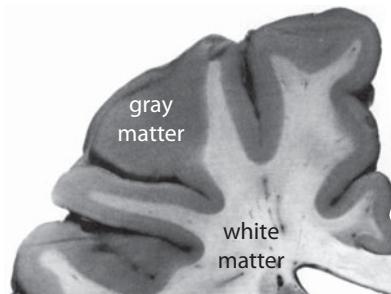


Figure 2-5. In fresh, meaning unstained, brain tissue, myelin lends a white appearance to regions where axons are numerous. Cell-dense regions, in contrast, appear gray. Therefore, the term gray matter refers to cell-dense regions, and white matter is a term that refers to regions containing a high density of myelinated axons. In this section through the cerebral cortex, the outer gray rind is the cerebral cortex and the underlying white matter contains axons on their way to and from the cerebral cortex.

Photograph reprinted with permission of deArmond S., et al. *Structure of the human brain: A photographic atlas*. New York: Oxford University Press, 1989.

CHAINS OF NEURONS AND INTERVENING SYNAPSES COMPRIZE NEURAL CIRCUITS AND PATHWAYS

Cells receive inputs from **afferents** and send **efferent** projections to target areas. Likewise, nuclei receive afferent input and send efferent projections (Fig. 2-6). Knowing the connections of a neuron is crucial to understanding that cell's function. For example, the lateral geniculate nucleus of the thalamus receives input from the retina and consequently it is no surprise that it is important to vision.

Within the central nervous system, neurons are connected by synapses. A cell that synapses onto another neuron is said to make a *direct connection*, whereas cells linked by more circuitous routes that include several synapses are

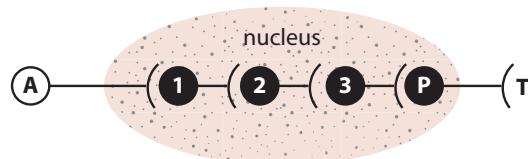


Figure 2-6. The term **nucleus** has two meanings. The first is the cellular organelle common to all eukaryotic cells. The second refers to a cluster of neuronal somata in the central nervous system that share a common function or functions. In this cartoon, circles represent cells. Dendrites are confined to the boundaries of a nucleus in some cases but extend beyond the boundaries in other cases. Note that dendrites are not drawn in order to simplify the drawing. Afferent input (A) to a nucleus arrives from cells outside of the nucleus. Interneurons (1, 2, 3) project to other cells in the same nucleus and projection neurons (P) carry the efferent output from the nucleus to target areas (T). When referring to single cells, the same terminology can be used. For example, cell 1 provides afferent input to cell 2 and cell 2 to cell 3 and so on. The efferent target of cell 1 is cell 2 and that of cell 2 is cell 3 and so on.

indirectly connected. In cases where we know how a number of neurons connect, we talk of **circuits** or **pathways**, with the former having a physiological connotation and the latter reflecting an anatomical entity.



ADDITIONAL READINGS

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CHAPTER 3

DEVELOPMENTAL OVERVIEW OF NEUROANATOMY: THE TUBE WITHIN THE BRAIN

An understanding of neuroanatomy gives you great powers, allowing you to diagnose many neurological problems. So, whether you are stuck on a desert island with a neurologically impaired companion, or your parent calls you to ask about their friend who seems to be slurring words, or you notice your patient's eyelid drooping, knowledge of neuroanatomy comes in handy. It helps you make a quick, inexpensive judgment-call: phone for an ambulance to the hospital, or watch and wait. After learning the material in this book—all of it rooted in an understanding of neuroanatomy—you will be able to distinguish a *go-directly-to-the-emergency-room* stroke from a *take-a-chill-pill* headache without the aid of a costly test. Combining a simple form of logic with neuroanatomy provides the basis for deciding whether the person who appears to choke and cough throughout meals is eating too fast or has a tumor pressing on a cranial nerve. All of us will have, and in fact already have had, close encounters with neurological dysfunction, such as persistent headaches or pain, fatigue, or nausea. Learning neuroanatomy dispels the overwhelming fear associated with neurological problems, allowing you to approach blurred vision, clumsiness, and dizziness with informed and sober deductive reasoning.

Although understanding neuroanatomy reaps great rewards, the complexity of the adult human brain overwhelms the beginning student. Here, we mitigate the challenge by following the development of the brain. We pick up our consideration of the brain at a stage when the structure of the primordial nervous system is simple.

NEURAL DEVELOPMENT PROVIDES A FRAMEWORK WITHIN WHICH TO UNDERSTAND NERVOUS STRUCTURE

The early embryo contains a homogeneous sheet of dividing cells that develop into a complex, patterned nervous system containing billions of neurons in the human. This phenomenal transformation from a simple sheet of cells to a complex structure serves as a roadmap to understand the basic anatomical organization of the brain. In this chapter, we follow as a small number of ectodermal cells proliferate and fold up into a tube, the basic shape of the adult vertebrate nervous system. By understanding that a simple tube of neural progenitor cells, termed the **neural tube**, expands in places, contracts in others, and turns here and there to shape the adult central nervous system (CNS), we gain an overall perspective of brain and spinal cord neuroanatomy. And we realize that, for all its complexity, the CNS is still simply a tubular structure at root. Please note that this chapter is intended as an introduction to CNS anatomy and that developmental *concepts* such as proliferation, stem cells, patterning, and signaling centers are covered only cursorily.

THE NERVOUS SYSTEM DEVELOPS FROM THREE REGIONS OF ECTODERM

Cells of the ectoderm, the most superficial germ layer of the embryo, on the dorsal side are induced to become neural cells and neural progenitor cells. Other ectodermal cells are induced to become epidermis. Three regions of ectoderm are specified that give rise to neurons and macroglia, as well as to a variety of non-neuronal tissues (Fig. 3-1). The three regions that give rise to all neurons and macroglia are:

- The neural tube derives from a sheet of **neuroectoderm** called the **neural plate** and runs most of the length of the embryo. The neural tube encircles a central lumen. The lumen becomes a series of **ventricles** in the adult (see Box 3-1). Neurons and macroglia of the CNS derive from neural tube progenitor cells. A small number of non-neuronal tissues, such as the **choroid epithelium** lining the brain's ventricles, the **pineal gland**, and the **septum pellucidum**, a thin membrane that separates the cerebral hemispheres anteriorly, also derive from neural tube.
- At the lateral edges of the neural plate, as it closes to form the neural tube, a group of motile cells called the **neural crest** develop (Fig. 3-1B). Neural crest cells migrate to specific locations throughout the body and head of the embryo. Neural crest-derived cells generate the bulk of the peripheral nervous system, glia and neurons alike, and also give rise to many non-neuronal tissues.

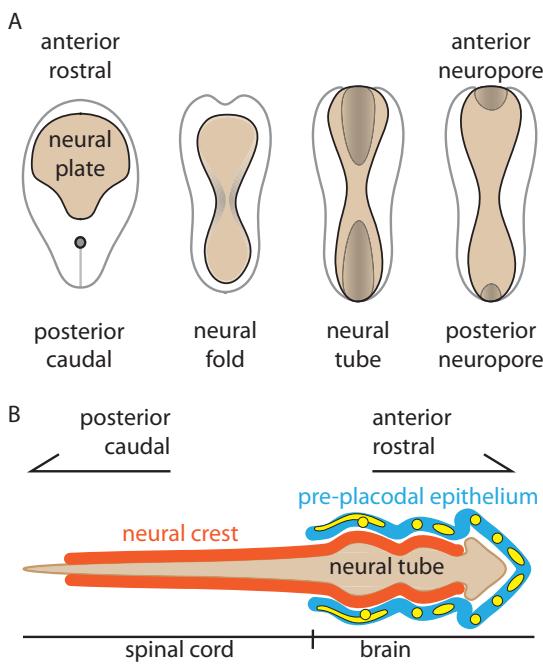


Figure 3-1. A: During the third week of gestation, the dorsal ectoderm forms the neural plate anterior to the node (dark circle). By the end of the third week, the neural plate has invaginated to make a neural fold, which then closes up to form a neural tube. Neural tube closure proceeds both rostrally and caudally from a starting point near the location of the future neck. Two openings, the anterior and posterior neuropores, are the last areas of the neural tube to close. B: This cartoon shows a dorsal view of the three-vesicle embryo with rostral to the right and caudal to the left. Immediately surrounding the neural tube is neural crest, which gives rise to most of the peripheral nervous system. Within the primordial head region of the developing embryo, neuroepithelium develops into pre-placodal ectoderm (blue area), which eventually populates seven bilateral pairs of placodes (yellow areas), five of which give rise to sensory neurons.

Box 3-1

THE VENTRICLES ARE EASILY RECOGNIZED ANATOMICAL LANDMARKS.

Ventricles are cerebrospinal fluid (CSF)-filled spaces at the center of brain tissue that serve as the brain's circulatory system (see Chapter 14). For the purpose of this chapter, the ventricles are most useful as easily recognized anatomical landmarks. As the ventricles in the different parts of the brain are distinctively shaped, the student can identify any brain region by simply identifying the ventricle present.

- **Placodes**, present in the head region only, flank the anterior neural crest and neural tube (Fig. 3-1B). Placodes, localized thickenings within the ectodermal layer, are the origin of many of the peripheral sensory neurons and glial supporting cells within the head as well as of several non-neuronal cell types.

In sum, *the nervous system derives from three embryonic sources, all of which arise from ectoderm*. The general rule is that neural tube gives rise to the CNS, whereas the peripheral nervous system arises from neural crest and placodes (see Box 3-2). Neural tube, neural crest, and placodes all also give rise to a number of non-neuronal tissues, some highly important to nervous system function and others not closely related to the nervous system.

PRIMARY AND SECONDARY NEURULATION FORM THE NEURAL TUBE

Neural plate cells proliferate and invaginate to form a **neural fold** or **groove** by 3 weeks of gestation (Fig. 3-1A). During the fourth week of human gestation, the neural fold closes off to form a tube around a central lumen, the future ventricular space. Ectodermal cells then proliferate and cover the neural tube dorsally, so that the tube is deep to overlying ectoderm, destined to become skin.

Neural tube closure, termed **primary neurulation**, starts at a site in the rostral embryo that will become the neck (see Box 3-3). Hours later, neural tube closure initiates at a second site, located at the very rostral end of the neural tube. In many mammals, including at least some human populations, neural tube closure may initiate at a third site, typically sited at the junction of the future hindbrain and midbrain. Neural tube closure proceeds bidirectionally from each initiation site until the length of the neural ectoderm is closed into a tube. Since tube closure initiates closer to the anterior than to the posterior end of the neuroectoderm, the **anterior** opening or **neuropore** closes a day or two before

Box 3-2

ONE GROUP OF CENTRAL NEURONS HAS A PLACODAL RATHER THAN NEURAL TUBE ORIGIN.

For virtually all of the cells of the nervous system, the rule that *neural tube gives rise to central nervous system and neural crest + placodes give rise to peripheral nervous system* holds. However, one curious group of placodal cells migrates into the central nervous system, differentiating into hypothalamic neurons that release **gonadotropin-releasing hormone**, a group of cells critical to growth, pubertal development, and reproductive function. Thus, one small group of central neurons has a placodal origin.

the **posterior neuropore**. When the neural tube between the anterior and posterior neuropores is closed, primary neurulation is complete.

The anterior neuropore ends up within the forebrain, but the posterior neuropore is located where the lumbar and sacral regions of the spinal cord meet. Subsequent to primary neurulation, **secondary neurulation** leads to the formation of the sacral spinal cord. *The end result of primary and secondary neurulation is a long tube of cells destined to be central neurons and glia surrounding a central ventricle* (Fig. 3-1B).

NEURAL CREST CELLS GENERATE THE PERIPHERAL NERVOUS SYSTEM AS WELL AS A NUMBER OF NON-NEURONAL TISSUES

Progenitor cells at the lateral edges of the neural plate (Fig. 3-1A) differ from those more medially positioned. Just before tube closure, these *motile* neural crest cells form bilateral proliferating streams that migrate widely through the developing embryo. *Neural crest progenitor cells give rise to most neurons of the peripheral nervous system* including:

- Most sensory neurons: neurons that reside in **spinal** and **cranial sensory ganglia** and respond to mechanical, thermal, and/or chemical stimulation of body tissues
- Autonomic ganglion neurons: neurons that control smooth muscle, cardiac muscle, and glands
- Enteric nervous system: about a billion neurons that form a little nervous system within the lining of the gut, possessing limited, but important, connections with the CNS
- Schwann cells: glial cells that wrap myelin around peripheral axons
- **Satellite cells**: the ganglionic equivalent of astrocytes, these glia support peripheral autonomic and sensory neurons

Neural crest cells also give rise to a number of brain-related tissues including but not limited to:

- Arachnoid and pia mater: the inner two layers of the meninges
- **Merkel cells**: neuroepithelial cells present in skin that sense and respond to pressure
- **Adrenal medullary chromaffin cells**: these cells located in the adrenal gland secrete **epinephrine**, also called **adrenaline**, in response to stress

Box 3-3

A FAILURE OF THE NEURAL TUBE TO CLOSE IS A COMMON BIRTH DEFECT.

Failures of the neural tube to form and close properly are termed **neural tube defects**, commonly abbreviated as **NTDs**. Some embryos with neural tube defects never come to term, being naturally aborted in the first trimester. In other cases, the neural tube forms but remains open in a spot. An open neural tube, either covered or not by skin, is a birth defect but not always a severe one.

Failure of the posterior neuropore to close results in **spina bifida**, a condition of variable severity. Some patients with spina bifida are asymptomatic, only learning of their condition after it is serendipitously discovered when a scan of the spine is performed for another reason. Other patients are paralyzed, unable to void, and suffer from **hydrocephalus**, a condition of fluid accumulation in the brain resulting in increased intracranial pressure.

Failure of the anterior neural tube to close causes a more consistently severe condition than that caused by failure of the posterior neuropore to close. It can result in **anencephaly**, a fatal condition, or any number of other conditions such as a partial externalization of the brain termed **encephalocele**. Failures to close off the anterior neural tube typically result in embryonic or neonatal fatality.

Proper neural tube closure, termed primary neurulation, requires **folic acid**, a dependence that may arise from the enormous cell proliferation required for tube closure and the critical role that folate plays in DNA replication and thus cell proliferation. Since primary neurulation completes by the end of the fourth week of gestation, at a time when many women do not yet know they are pregnant, folate supplements directed at the prenatal market would be largely ineffective. As a result, several countries, including the United States and Canada, have required folic acid supplementation of grain products such as breakfast cereals since the 1990s. This approach of ensuring sufficient folate intake among child-bearing women and the general population alike has resulted in a precipitous decline in the prevalence of NTDs. However, NTDs continue to occur, even in countries with folate supplementation programs. In part, this is due to inadequate consumption of folate-supplemented foods. Further, some NTDs occur even despite adequate folate intake. Recent evidence suggests that, at least in some cases, these defects may be rescued by supplemental **inositol**.

Finally, the neural crest gives rise to a number of non-neuronal tissues such as the aorta, melanocytes, the cornea, dentin-producing odontoblasts, cells that direct inner ear development, and facial muscles, bones, and tendons. Because of the diverse cellular fates of neural crest cells, disorders in crest development exhibit phenotypes that involve disruption of numerous and widespread crest-derived tissues (see Box 3-4). Neural crest-related disorders often stem from a single genetic defect but include complex symptoms, each representing dysfunction in one of the numerous and diverse progeny of the neural crest.

PLACODES GIVE RISE TO IMPORTANT SENSORY STRUCTURES IN THE HEAD

Lateral to the neural crest of the most anterior part of the embryo and anterior to the neural tube, a strip of ectoderm thickens into **pre-placodal ectoderm**. Pre-placodal ectoderm interacts with local mesodermal signals to form seven pairs

PATIENTS WITH WAARDENBURG SYNDROME HAVE A DEFECT IN NEURAL CREST DEVELOPMENT.

Patients with **Waardenburg syndrome** have dominantly inherited mutations in any of several genes that regulate neural crest development. These patients present with several symptoms that appear unrelated to each other until one realizes that all derive from disruption of normal neural crest development. Predominant symptoms of Waardenburg syndrome include some degree of deafness, lack of pigment in areas of the skin and hair, and an abnormal facial appearance. The deafness probably occurs because inner ear development, normally directed by neural crest-derived cells, is disrupted. The lack of pigmentation can be accounted for by a problem with neural crest-derived melanocytes, and the abnormal appearance by changes in facial bones, muscles, and tendons derived from neural crest. Some patients exhibit additional neurological problems such as digestive problems associated with incomplete development of the enteric nervous system. Waardenburg syndrome exemplifies developmental disorders in their at-first-glance odd but at-second-glance logical collection of symptoms related to each other solely by a common developmental origin.

of placodes (yellow regions in Fig. 3-1B), five of which give rise to sensory neurons. Two of the placodes, the **lens** and **hypophyseal placodes**, give rise to the lens (of the eye) and **anterior pituitary**, respectively, but do not bear any neuronal or glial cells. Note that the anterior pituitary is the non-neural portion of the pituitary (see Chapter 13). Thus, like both neural tube and neural crest, placodes give rise to a variety of non-neuronal as well as neural cell types.

There are five sets of placodes from which sensory neurons are derived:

- **Nasal placodes** give rise to olfactory sensory neurons.
- **Otic placodes** give rise to auditory and vestibular primary sensory afferents that carry information about sound and head acceleration, respectively, from the inner ear into the CNS.
- **Ophthalmic placodes** give rise to primary sensory afferents that carry information about touch, pain, and temperature arising from the eye and forehead.
- **Trigeminal placodes** give rise to primary sensory afferents that carry information about touch, pain, and temperature arising from the face below the eye and forehead.
- **Epibranchial placodes** give rise to primary sensory afferents that carry sensory input from much of the viscera.

Each of the above placodes gives rise to cell types beyond primary afferent neurons, including satellite cells and non-neuronal sensory neurons, such as **hair cells** that respond to sound and head acceleration.

THE NEURAL TUBE GROWS, BULGES AND CONTRACTS TO FORM THE FIVE MAJOR DIVISIONS OF THE CENTRAL NERVOUS SYSTEM

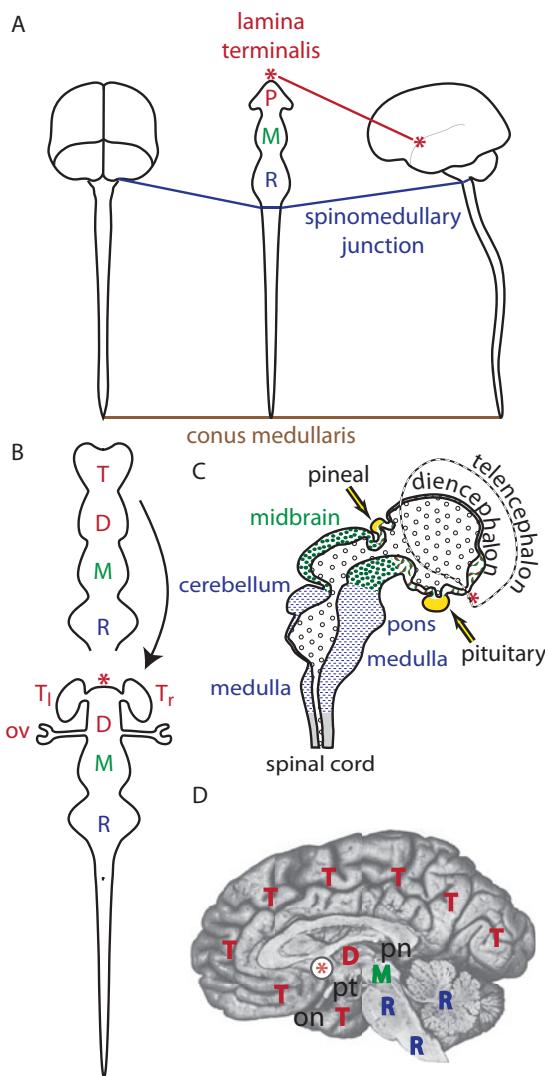
Once completely formed by neurulation, the neural tube reaches from a caudal point that will eventually become the **conus medullaris**, or caudal end of the spinal cord, rostrally to the **lamina terminalis**, the rostral end of the neural tube, which ends up located deep within the adult human brain (Fig. 3-2). Here, we follow the developmental process by which the lamina terminalis becomes buried within the cerebrum and thereby enable the reader to better understand and visualize brain anatomy.

At the end of the fourth gestational week, the neural tube contains three bulges or **vesicles** at its rostral end (Fig. 3-2A). The three vesicles destined to become the brain are, from front to back:

- **Prosencephalon** or forebrain
- **Mesencephalon** or midbrain
- **Rhombencephalon** or hindbrain

Figure 3-2. Brain development proceeds from a three-vesicle stage (A) consisting of the prosencephalon (P), mesencephalon (M), and rhombencephalon (R) to a four-vesicle stage (B). The rostral end of the neural tube, the lamina terminalis (*), ends up as the most rostral point in the adult diencephalon, a site that is buried deep within the expansion of the overlying telencephalic hemispheres (right panel in A). The caudal end of the neural tube becomes the conus medullaris, the caudal tip of the spinal cord. The junction between the developing spinal cord and rhombencephalic vesicle is the **spinomedullary junction**, where the spinal cord and hindbrain meet in the adult. In the four-vesicle stage (B), the prosencephalon has divided into the caudally located diencephalon (D) and the rostral telencephalon (T). Soon after forming, the telencephalic vesicle invaginates along the midline to form the left (T_l) and right (T_r) hemispheres (B). The telencephalic hemispheres expand laterally, rostrally, and eventually caudally to cover the diencephalon in the adult (D). From the diencephalon emerges the optic vesicle (ov in B) which will develop into the optic nerve (on in D) and retina. The lumen within the developing brain changes from a simple tube to a space with various bulges, nooks, and crannies. The mid-sagittal cartoon in C shows how the embryonic lumen bulges out within the rhombencephalon (blue), mesencephalon (green), and diencephalon in the four-vesicle human brain at about 12 weeks of age. The lumen within the telencephalic hemispheres is not illustrated here for clarity. The developing telencephalic hemispheres (dashed line) cover most of the diencephalon in a 12-week human embryo. The pineal and pituitary glands (yellow) emerge from the diencephalic vesicle. In the adult brain (D), the pineal (pn) attaches to the dorsal surface of the diencephalon (red D) and the pituitary (pt) to the ventral surface. Finally, the rhombencephalic vesicle gives rise to the cerebellum, which is only partially developed at the embryonic stage illustrated.

Photograph in D reprinted with permission of deArmond S., et al. *Structure of the human brain: A photographic atlas*. New York: Oxford University Press, 1989.



The most caudal portion of the neural tube develops into the spinal cord. The level at which the rhombencephalon and spinal cord meet develops into the spinomedullary junction, which is located at the foramen magnum in the adult.

At about the fifth week of gestation, the prosencephalon divides into the **telencephalon** and the **diencephalon** (Fig. 3-2B). Soon after developing from the prosencephalon, the single telencephalic vesicle invaginates at the midline to become two telencephalic hemispheres (see more below). In the adult, the telencephalon includes both hemispheres of cerebral cortex, the core components of the basal ganglia, and the **amygdala**. The diencephalon contains the thalamus and hypothalamus and gives rise to two outpouchings called the **optic vesicles**. The stalk of the optic vesicles becomes the **optic nerve**, and the cup at the end of the outpouching becomes the **retina** (see Box 3-5). The retina is composed of the **neural retina** and the non-neuronal **pigment epithelium** (see Chapter 16).

Box 3-5

THE RETINA IS PART OF THE CENTRAL NERVOUS SYSTEM, DERIVED FROM THE DIENCEPHALON.

The retina is the most accessible part of the CNS and is considered a “window to the brain.” Therefore, the central nervous system (CNS) can be readily and noninvasively visualized by viewing the retina through an ophthalmoscope. Insults that profoundly impact brain function globally, such as increased cranial pressure, will cause obvious changes in the appearance of the retina, making the appearance of the retina an important diagnostic tool.

The rhombencephalon develops into the adult pons, medulla, and cerebellum (Fig. 3-2C). The anterior third or so of the hindbrain gives rise to the pons and cerebellum, whereas the posterior portion of the hindbrain develops into the medulla.

By the end of the fifth week, the embryonic human brain contains four vesicles. From rostral to caudal:

- Telencephalon ≈ cerebral cortex, basal ganglia, amygdala
- Diencephalon ≈ thalamus, hypothalamus, retina
- Mesencephalon = midbrain
- Rhombencephalon = hindbrain = pons, medulla, and cerebellum

The spinal cord and the four regions of the brain comprise the five divisions of the CNS (Fig. 3-2D).

THE LUMEN OF THE NEURAL TUBE DEVELOPS INTO THE ADULT VENTRICULAR SYSTEM

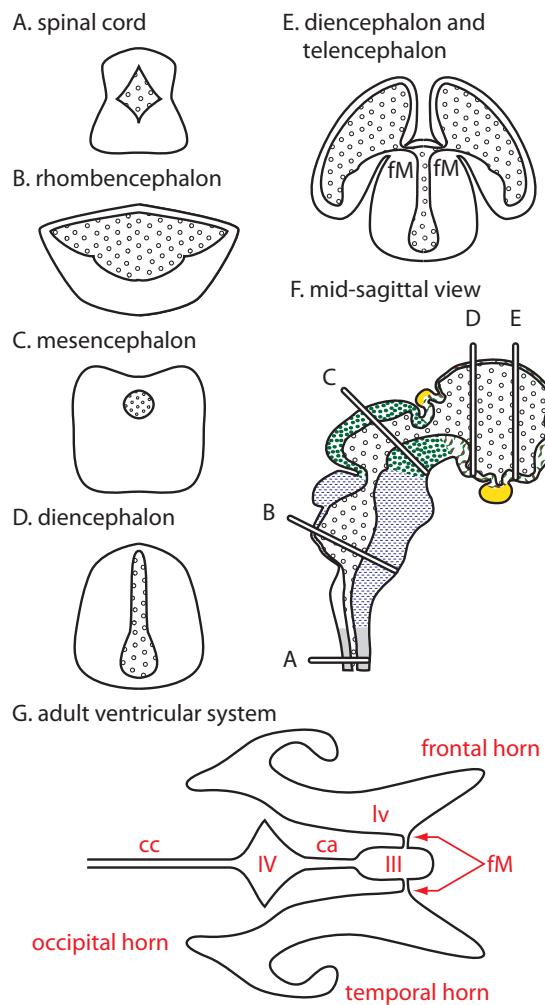
Neural progenitor cells are located next to the inner lumen that runs the length of the embryonic neural tube. The embryonic lumen expands, bulges, and cinches along with corresponding changes in the shape of the neural tube and eventually develops into the cerebrospinal fluid (CSF)-filled ventricular system of the adult. As our goal here is to use development to understand brain neuroanatomy, we now fast-forward from the embryonic neural tube to the adult brain to learn the eventual fate of the embryonic lumen at different points along the neuraxis (Fig. 3-3).

The spinal cord surrounds a central lumen called the **central canal**. Just rostral to the spinomedullary junction, the central canal opens into the **fourth ventricle**, the ventricle present in the hindbrain. The fourth ventricle occupies the space between the medulla and pons ventrally and the cerebellum dorsally. If we removed the cerebellum and viewed the fourth ventricle from above, we would see a depression, or **fossa**, shaped like a diamond or rhombus (see region marked IV in Fig. 3-3G). Consequently, the space occupied by the fourth ventricle is often referred to as the **rhomoid fossa**.

At the junction of the rhombencephalon and mesencephalon, the fourth ventricle narrows into a thin channel. This channel, present in the midbrain only, is called the **cerebral aqueduct**. The narrow cerebral aqueduct links the fourth ventricle to the **third ventricle** present on the midline of the diencephalon.

As mentioned above, the human telencephalic vesicle invaginates along the dorsal midline to form two dorsal telencephalic halves or **hemispheres**, which will eventually develop into the two cerebral hemispheres (Fig. 3-2B).

Figure 3-3. Cross-sections through the embryonic spinal cord (A), hindbrain (B), midbrain (C), diencephalon (D, E), and telencephalon (E) show that progenitor cells surround a central lumen at every level of the neuraxis. Although the lumen takes different shapes, it is always located on the midline in the spinal cord, hindbrain, midbrain, and diencephalon. However, the telencephalic hemispheres are located lateral to the diencephalon, and consequently, the lumen divides and courses laterally into each telencephalic hemisphere. The narrow foramen of Monro (*fM*) connects the lumen of the diencephalon to the lumen of each telencephalic hemisphere. F: A mid-sagittal view through the developing human brain shows the approximate level of each cross section (A–E). G: A cartoon of the ventricular system, viewed from above, shows the adult fate of the lumen at each level of the embryonic neural tube. The lumen of the embryonic spinal cord becomes the central canal (*cc*), which is not patent in the adult mammal. The lumen of the rhombencephalon becomes the fourth ventricle (*IV*) and that of the mesencephalon becomes the narrow cerebral aqueduct (*ca*). The lumen of the diencephalon becomes the third ventricle (*III*), and the lumen in each adult telencephalic hemisphere is a lateral ventricle (*lv*), connected to the third ventricle by the foramen of Monro (*fM*). In humans, the lateral ventricle is greatly expanded to accommodate the extensive cerebral cortex and stretches rostrally into the frontal lobe (frontal horn) and caudally into the occipital lobe (occipital horn), and also curves around into the temporal lobe (temporal horn).



The invagination, present by the sixth week of gestational development, separates the lumen, as well as the two hemispheres. Consequently, each hemisphere has its own lumen, which develops into a **lateral ventricle** (Fig. 3-3E). In the adult, each lateral ventricle links to the third ventricle through a short, narrow strait called the **foramen of Monro**.

Cerebrospinal fluid is critical to the functioning of the CNS, and therefore no region of the brain or spinal cord can be too far from a CSF source. In the case of the spinal cord, the central canal is occluded in the adult mammal. Consequently, CSF is supplied to the cord solely by the surrounding subarachnoid space. The CSF supply to the brain arises from both the ventricles and the surrounding subarachnoid space. The fourth ventricle, cerebral aqueduct, and third ventricle carry CSF to the hindbrain, midbrain, and diencephalon, respectively. In the telencephalon, the situation grows more complicated because of the large expansion in telencephalic territory in humans and other primates. To accommodate the expanded cerebral cortex, the lateral ventricle in each hemisphere extends along every axis of telencephalic growth. This means that the lateral ventricles extend rostrally into the frontal lobe, caudally

into the occipital lobe, and then curve around and pass through to the **temporal pole** or tip of the temporal lobe (Fig. 3-3G).

DEVELOPMENTAL TERRITORIES CONFER A BASIC FUNCTIONAL ORGANIZATION TO THE BRAIN AND SPINAL CORD

Within each division of the CNS, areas with different functions in the adult arise from different embryonic territories. This is most clearly illustrated in the spinal cord. In the embryonic cord, the central lumen has bilateral inflection points or indentations. Each inflection point, termed the **sulcus limitans** (Fig. 3-4), separates the embryonic spinal cord into dorsal and ventral halves (see Box 3-6). Cells in the dorsal **alar plate** are destined to serve largely sensory functions, and those in the ventral **basal plate** serve motor functions in the adult (Fig. 3-4A). Thus, primary sensory afferents enter the spinal cord from the dorsal side and terminate in the dorsal part of the spinal gray matter. Motoneurons innervating skeletal muscles have somata in the ventral portion of the spinal gray and send an axon out from the ventral spinal surface. Just ventral to the sulcus limitans, the somata of autonomic motor neurons are located.

The dorsal covering of the neural tube opens up in the hindbrain as the fourth ventricle replaces the central canal. At this point, the sulcus limitans is still visible as an inflection point in the hindbrain (hollow arrowhead Fig. 3-4B). Further, the sulcus limitans in the hindbrain still separates the alar plate, giving rise to cells serving sensory functions, from the basal plate serving motor functions. The only difference is that, because of the opening of the fourth ventricle, *dorsal* within the spinal cord corresponds to *lateral* in the hindbrain and *ventral* in the spinal cord corresponds to *medial* in the hindbrain. Thus, brainstem cells with a sensory function are lateral, rather than dorsal, to cells with a motor function. One more group of cells is noteworthy. Cells that border the hindbrain roof plate form the **rhombic lip** (Fig. 3-4B). The rhombic lip, as well as the roof of the fourth ventricle, generate the cells that populate the cerebellum and the choroid epithelium of the fourth ventricle (see Box 3-7). Neurons that give rise to precerebellar nuclei, meaning nuclei that provide input to the cerebellum, also arise from the rhombic lip and migrate to final positions within the pons and medulla.

Within the embryonic diencephalon, the inflection point in the lumen corresponds to the **hypothalamic sulcus** (Fig. 3-4C). Dorsal to the hypothalamic sulcus, cells are destined to become the thalamus, also called **dorsal thalamus**, and ventral to the sulcus, cells give rise to the hypothalamus.

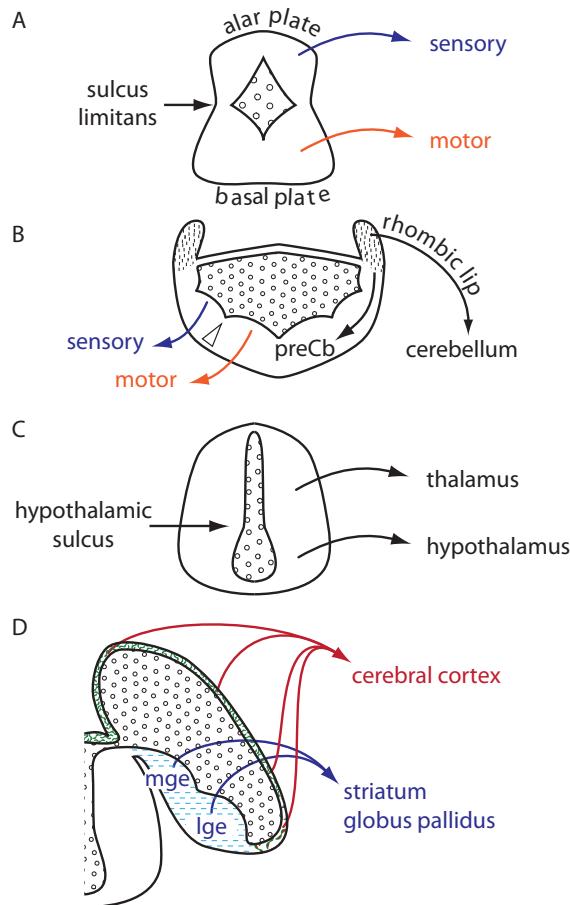
The embryonic telencephalon has distinct dorsal and ventral territories (Fig. 3-4D). Dorsally, a thin rind of tissue is destined to become the cerebral cortex. Ventrally, telencephalic tissue is amassed into bulges called **ganglionic eminences**. The territory occupied by the **medial** and **lateral ganglionic eminences** becomes **striatum** and **pallidum**, the two core structures of the basal ganglia (see Box 3-8).

Box 3-6

WHEN APPLIED TO THE HUMAN SPINAL CORD, THE TERMS ANTERIOR AND VENTRAL ARE SYNONYMOUS AS ARE POSTERIOR AND DORSAL.

To accommodate our upright posture, the human brain and spinal cord are oriented at right angles to each other. This change results in a change in the meaning of directional terms within the brain and spinal cord of humans relative to quadrupeds (see Fig. 1-4). A corresponding difference exists between the names for structures commonly used by clinicians and by basic scientists. In this book, the basic terms are employed and the clinical terms mentioned. This approach will allow the reader to understand the scientific literature by clinicians and basic scientists alike.

Figure 3-4. In the spinal cord (A), a distinct inflection point, the sulcus limitans, separates the alar plate, destined to give rise to neurons that receive input from primary sensory afferents, from the basal plate that gives rise to motoneurons, autonomic motor neurons, and motor interneurons. In the hindbrain (B), the sulcus limitans (arrowhead) again separates cells destined for a sensory role from those destined to become motor-related. Cells in the rhombic lip give rise to the cerebellum and to hindbrain nuclei that provide direct input to the cerebellum (*preCb*). The cells that give rise to the cerebellum are located in the rostral rhombic lip region. Therefore, the cerebellum grows back, from the rostral part of the rhombencephalon, destined to become the pons, back over the caudal part of the rhombencephalon, destined to become the medulla. As a result, the cerebellum is attached to the pons but simply overhangs the medulla without an attachment. In the diencephalon (C), the hypothalamic sulcus separates the territories of cells destined to become hypothalamus and thalamus. In each telencephalic hemisphere (D), the thin rind of the dorsal telencephalon becomes the cerebral cortex, whereas the lateral and medial ganglionic eminences (*lge*, *mge*) develop into the striatum, pallidum, and at least parts of the amygdala.



Box 3-7

CHOROID EPITHELIUM JOINS WITH PIA TO FORM CHOROID PLEXUS.

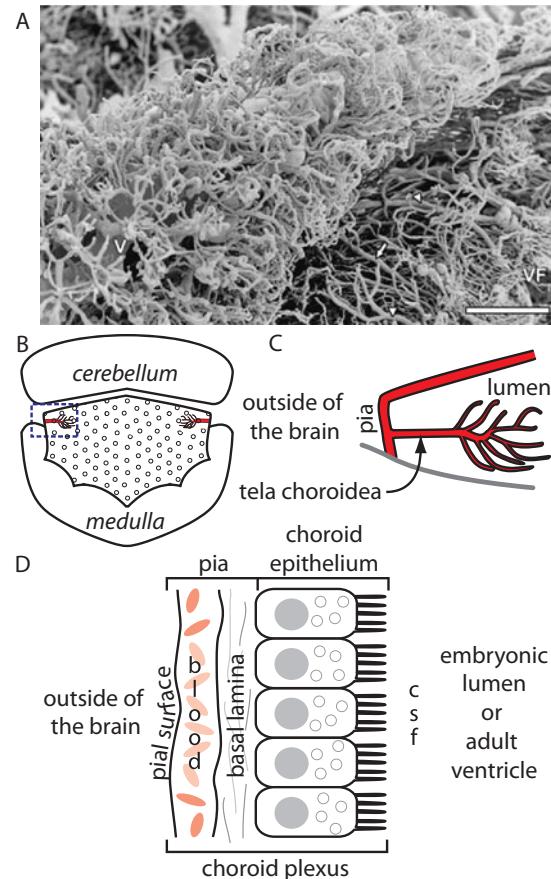
Choroid epithelium is a specialized type of cuboidal epithelium that forms a plexus with capillaries in the pia. This plexus is termed **choroid plexus**. Choroid plexus forms at specific locations in the fourth ventricle, third ventricle, and lateral ventricles and, in the adult, produces cerebrospinal fluid or CSF. Choroid plexus forms where the wall of the neural tube thins out (Fig. 3-5). For example, in the rhombencephalon, the roof of the neural tube opens up and is covered by pia. At sites where choroid plexus will develop, the pia forms an outpouching that is rich with capillaries. This vascular fold divides into

an intricate system of tiny branches with protuberances called **villi**. Choroid epithelium covers the ventricular side of the pial capillaries and filters the fluid that flows out of the capillaries. This filtered fluid is CSF.

Choroid plexus forms an interface between the inside and outside of the brain. Therefore, wherever you see choroid plexus, remember that on one side is a ventricle and on the other is the outside of the brain. This simple rule helps orient even the most experienced neuroanatomist to forebrain anatomy.

Figure 3-5. A: A scanning electron micrograph shows the developing choroid plexus in the embryonic lumen of the neural tube of a 20-week-old human fetus. The choroid plexus of the embryo is simpler than that of the adult with far fewer villi present. B–C: Choroid plexus develops in specific areas of the developing neural tube. In the caudal rhombencephalon, the lumen between the areas that will develop into the medulla and cerebellum is shown. The area in the dotted box in B is shown at larger magnification in C. The pia of the roof plate forms outpouchings into the lumen. D: The outpouching of vascularized pia is lined with choroid epithelium. Choroid epithelial cells have small protuberances called **microvilli** on their apical surface. Due to hydrostatic pressure, blood from the capillaries of the pia traverses the basal lamina and is filtered by the choroid epithelium to produce cerebrospinal fluid (CSF) in the adult. In the embryo, the filtered fluid resembles but is not identical to CSF in the adult. The outside of the brain is located on the pial side of choroid plexus, and a lumen or ventricle is located on the choroid side.

Photomicrograph in A is reprinted from Zagorska-Swiezy, K., Litwin, J. A., Gorczyca, J., Pitynski, K., Miodonski, A.J. The microvascular architecture of the choroid plexus in fetal human brain lateral ventricle: A scanning electron microscopy study of corrosion casts. *J Anat* 213: 259–265, 2008, with permission of the publisher, John Wiley & Sons.



THE TERRITORY ALLOTTED TO THE DORSAL TELENCEPHALON IS GREATLY EXPANDED IN THE HUMAN

In the human and many other mammals, the proliferation of telencephalic progenitor cells produces an enormous number of neurons, counted in the billions. To accommodate all of the cells produced, the territory of the human cortex is greatly expanded compared with the cortex of most other mammals such as rodents. In part, the expansion takes the form of the cortex growing caudally back over the thalamus and brainstem (Fig. 3-6). The dorsal telencephalic tissue expands so much that the cerebral cortex covers the diencephalon, midbrain, and part of the hindbrain, obscuring the fundamentally tubular structure of the brain. Yet, even this caudal telencephalic expansion yields insufficient territory for the human cerebral cortex. In the human and a few other primates, the cortex populates a bulge of tissue that curves around to form the temporal lobe (Fig. 3-6B). The temporal lobe serves

Box 3-8

NEURONS OFTEN MIGRATE FROM THE SITE WHERE THEY ARE BORN TO THE SITE THAT THEY OCCUPY IN THE ADULT BRAIN.

Many cells in the embryonic neural tube migrate from the place where they are born to their final location in the mature brain. For example, a population of cells in the medial ganglionic eminence ends up as interneurons in the cerebral cortex. As another example, at least one group of amygdala

cells migrates in from the dorsal telencephalon. Despite these examples, *most* cells in the dorsal telencephalon stay in the cerebral cortex and *most* cells in the ganglionic eminences stay **subcortical**, or deep to the cerebral cortex. The statements in the text reflect the fate of the bulk of the cells involved.

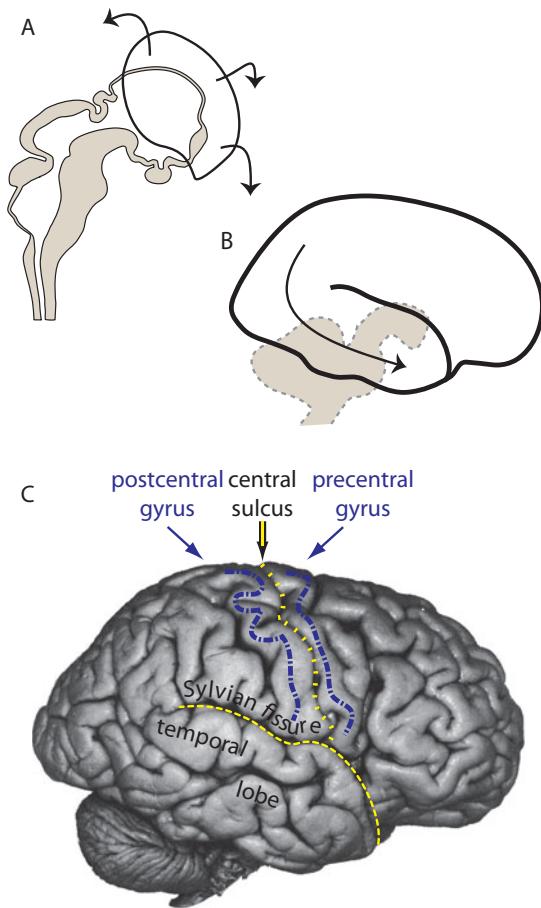


Figure 3-6. In the human, the cerebral cortex is greatly expanded. **A:** Embryonic dorsal telencephalic tissue grows in all directions until it covers the diencephalon and mesencephalon completely. **B:** In the adult, the anterior part of the cerebellum, part of the hindbrain, is also covered by cerebral cortex. Temporalization, the expansion of cerebral cortex to form a temporal lobe, reaches a zenith in humans, allowing for more neural tissue devoted to language, face recognition, and factual memory. The temporal lobe is separated from the parietal and frontal lobes by the Sylvian fissure. **C:** The surface area of the cerebral cortex is greatly increased by gyration, which produces sulci (blue) and gyri (yellow). For example, the central sulcus runs from the dorsal midline to the Sylvian fissure and divides the precentral gyrus in the frontal lobe from the postcentral gyrus in the parietal lobe.

Photograph in C reprinted by permission of deArmond S., et al. *Structure of the human brain: A photographic atlas*. New York: Oxford University Press, 1989.

quintessentially human functions such as complex verbal communication, face recognition, and factual memory.

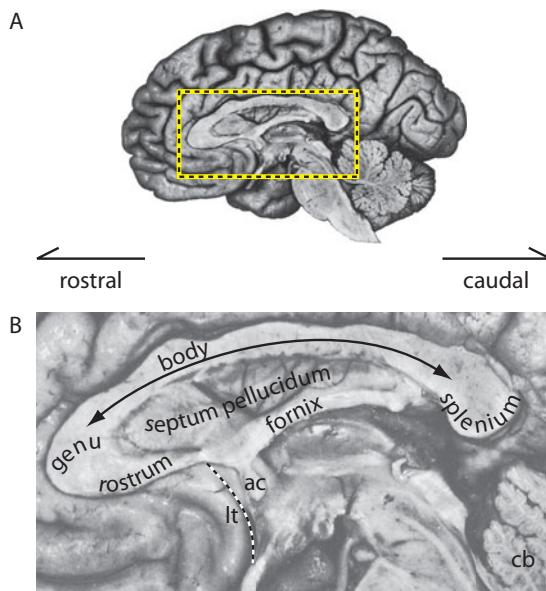
The telencephalon utilizes one more trick to maximize the amount of space available for cerebral cortex within the limited confines of the skull. In the human, and some other mammals, the dorsal telencephalon invaginates into **sulci** (**sulcus** is the singular form), or chasms, and **gyri** (**gyrus** is the singular form), or ridges (Fig. 3-6C). Such **gyrification**, which is extensive in humans, greatly increases the surface area of the cortex, so that in the human, only about a third of the cerebral cortex is exposed on the outer surface, with the remainder buried within the sulci. By contrast, the cortex of a mouse, for example, is small and **lissencephalic**, or smooth.

THE CORPUS CALLOSUM BRIDGES THE TELENCEPHALIC HEMISPHERES

The gray matter regions of the two telencephalic hemispheres remain physically separate, divided by a fold of dura called the **falx cerebri**. The telencephalic hemispheres are however connected by a large **commissure**, a white matter tract that connects the two sides of the nervous system (Fig. 3-7). The commissure connecting gray matter in the dorsal telencephalic hemispheres is called the **corpus callosum** (see Box 3-9). The corpus callosum contains axons originating in the cerebral cortex on one side destined for the *corresponding* area of cortex in the opposite hemisphere. For example, neurons in frontal cortex send axons across the interhemispheric divide through the anterior portion of the corpus callosum to the frontal cortex in the contralateral, or opposite, frontal cortex. Similarly, corresponding areas of parietal, temporal, and occipital cortex are also connected through the corpus callosum. In this way, most regions of cerebral cortex are connected with their

Figure 3-7. The corpus callosum is the major commissural tract that carries axons linking the two cerebral hemispheres. The box on the mid-sagittal section in A shows the area that is magnified in B. The corpus callosum is divided into the **rostrum**, **genu**, **body**, and **splenium**. The rostrum of the corpus callosum tapers out and ends at the lamina terminalis (dashed line labeled *lt*). Deep to the corpus callosum is a thin membrane called the **septum pellucidum**, a non-neuronal tissue derived from neural tube, and deep to the septum pellucidum is the fornix, which carries efferents from the hippocampal formation bound for the mammillary bodies. The anterior commissure (*ac*) connects corresponding regions in the left and right temporal lobes. The cerebellum (*cb*) is labeled for orientation.

Photographs reprinted by permission from deArmond S., et al. *Structure of the human brain: A photographic atlas*. New York: Oxford University Press, 1989.



THE CORPUS CALLOSUM FORMS A MAJOR CONDUIT FOR TRANSFER OF INFORMATION BETWEEN THE TWO CEREBRAL HEMISPHERES.

The corpus callosum allows the two cerebral hemispheres to interact and seamlessly function with a common purpose. In work that earned him the 1981 Nobel Prize in Physiology or Medicine, Roger Sperry demonstrated that each cerebral hemisphere *can* function autonomously. In fact, people or animals with a severed corpus callosum, termed **split brain**, appear normal even upon initial examination. Similarly, people born without a corpus callosum due to **agenesis of the corpus callosum** are typically normal as long as no other developmental deficits accompany the failure of the corpus callosum to form. The work of Sperry and others further showed that the two hemispheres have some divergent roles, with language production centered in the left hemisphere and image-derived reasoning in the right hemisphere.

Functional deficits in split-brain animals or people become evident using sophisticated tests that restrict input and output to opposite hemispheres.

For example, if you ask a split-brain patient to view an object located in their left **visual field** (meaning to the left of where the patient is looking), the patient will be unable to name the object. This is because the left visual scene is represented in the right occipital cortex, whereas language skills require the left hemisphere, at least in the majority of people. Without the corpus callosum, visual information about the object, located in the right hemisphere, cannot access language production centers in the left hemisphere. Such experiments with split-brain patients demonstrate that, normally, the corpus callosum furnishes interhemispheric communication.

Although the corpus callosum is the major conduit for interhemispheric communication, it is not the only one. Additional commissures, or connections between the two sides of the nervous system, include the **anterior commissure**, **posterior commissure**, **optic chiasm**, and **hippocampal commissure** in the brain and the **anterior white commissure** in the spinal cord.

contralateral partners through the corpus callosum. Notable exceptions are the hippocampus and other parts of the temporal lobe, which connect through the **hippocampal commissure** and **anterior commissure** (Fig. 3-7), respectively.

A major fiber tract called the **internal capsule** physically links the telencephalon to the diencephalon in the adult (Fig. 3-8). The internal capsule travels along a course that passes between the medial edge of the ventral telencephalon and the lateral edge of the diencephalon. Most of the axons, or fibers, in the internal capsule descend from the cerebral cortex to lower parts of the CNS (see Chapter 13). The remaining axons in the internal capsule travel from the thalamus to the cerebral cortex.

TEMPORALIZATION RESULTS IN SEVERAL FEATURES WITHIN THE HUMAN TELENCEPHALON ADOPTING A C-SHAPE

Temporalization refers to the expansion of cerebral cortex to form a temporal lobe. The lateral ventricle in each telencephalic hemisphere follows the general outline of the cerebral hemispheres and thus resembles a C-shape in the

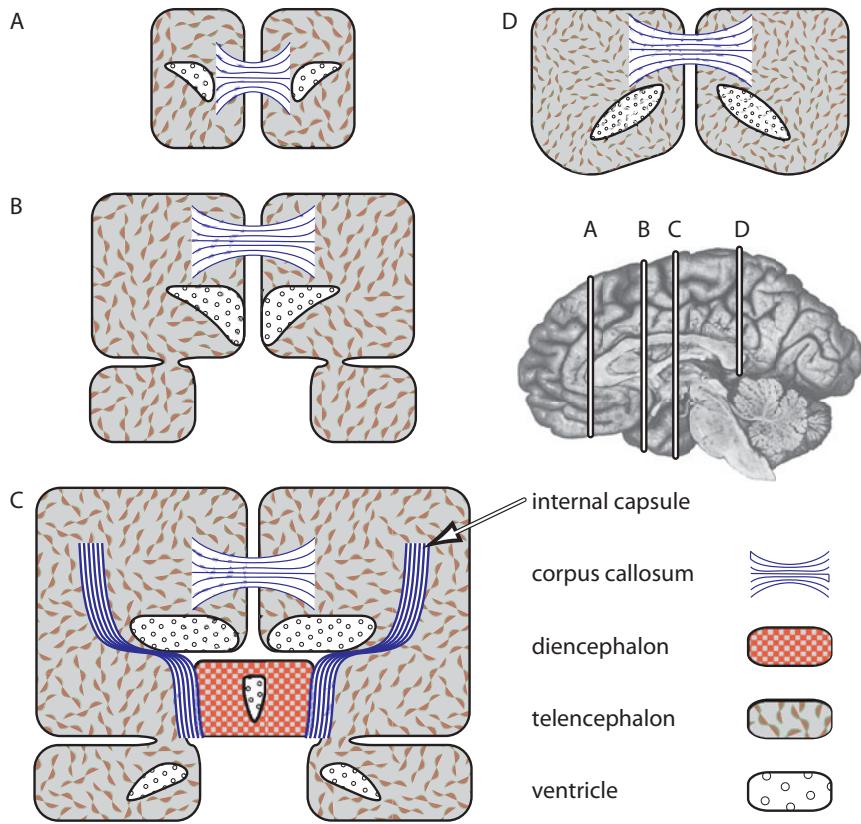


Figure 3-8. A series of cartoons show the anatomical relationships between the diencephalon and the two telencephalic hemispheres. The telencephalon quickly splits into two telencephalic hemispheres, which stay largely separate. However, a number of commissures contain axons that cross between the two hemispheres. The largest of these commissures is the corpus callosum, which extends from the frontal lobe to the occipital lobe. In the rostral frontal lobe (A), the two telencephalic hemispheres, each containing a lateral ventricle, are connected by the corpus callosum. Just anterior to the lamina terminalis (B), the two telencephalic hemispheres, each with a lateral ventricle, are connected by the corpus callosum. At this level, the very anterior portion of the temporal lobe, anterior to the temporal pole of the lateral ventricle, is present but separated from the frontal and parietal lobes by the Sylvian fissure. Caudal to the lamina terminalis (C), the corpus callosum connects the telencephalic hemispheres, and the internal capsule forms a physical link between the telencephalic hemispheres and the diencephalon. Thus, although the adult diencephalon and telencephalon arise from different embryonic vesicles, they are joined by the internal capsule. Finally, in the caudal forebrain, the corpus callosum connects the telencephalic hemispheres. At this level, the cerebellum is located ventral to the forebrain, separated by a fold of the dura called the **tentorium cerebelli**, or simply the **tentorium**. Note that the structures illustrated are not to scale but are sized to most clearly illustrate the essential relationships. The photograph shows the approximate level of the cartoons illustrated in A–D. Photograph reprinted by permission from deArmond S., et al. *Structure of the human brain: A photographic atlas*. New York: Oxford University Press, 1989.

temporalized human brain (Fig. 3-3). Several telencephalic structures follow the C-shape of the lateral ventricle (Fig. 3-9). Recall that the internal capsule travels between the diencephalon and ventral telencephalic structures. En route, the internal capsule runs through the striatum, dividing the striatum into a mediiodorsal component called the **caudate** and a ventrolateral component called the **putamen**. The caudate hugs the lateral ventricle, so that the caudate forms a C-shape as well. The **fornix** is an important axonal pathway from the hippocampus—a cortical region required for memory formation—to the **mammillary bodies** on the ventral surface of the diencephalic hypothalamus, also critical for memory. The fornix travels a C-shaped path along the lateral ventricle (Fig. 3-9).

One outcome of the dorsal telencephalic expansion is that there exists a space that is external to the **meninges**, and therefore is outside of the brain, even though it is

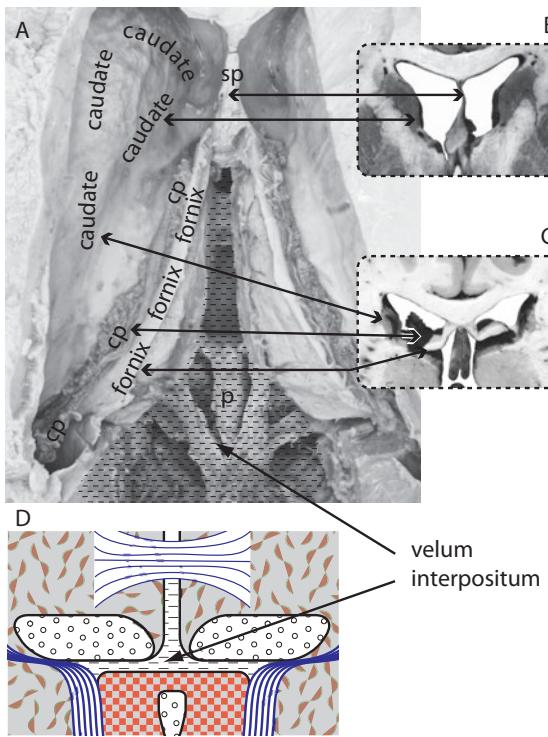


Figure 3-9. A: The C-shape of the lateral ventricle and associated structures can be seen in this dissection of the human brain. The dorsal cerebral cortex, corpus callosum, and roof of the lateral ventricles have been removed. This photomicrograph shows the view as one looks down on the brain, with rostral located at the top of the figure and caudal at the bottom. The caudate, choroid plexus (*cp*), and fornix all follow the curvature of the lateral ventricles. The double arrows point to the caudate, septum pellucidum (*sp*), choroid plexus, and fornix in the coronal plane (B, C). The lateral ventricle occupies the space above the caudate. The area with the dashed pattern is the velum interpositum. The pineal gland (*p*) and the internal cerebral veins (running down the sides) fill the velum interpositum. D: A magnified view of the cartoon from Figure 3-8C shows that the velum interpositum lies between the telencephalic hemispheres, the diencephalon, and the corpus callosum.

Photograph in A reprinted by permission of Bruni, J.E., and Montemurro, D. *Human neuroanatomy: A text, brain atlas, and laboratory dissection guide*. New York: Oxford University Press, 2009. Photographs in B and C reprinted by permission of deArmond S., et al. *Structure of the human brain: A photographic atlas*. New York: Oxford University Press, 1989.

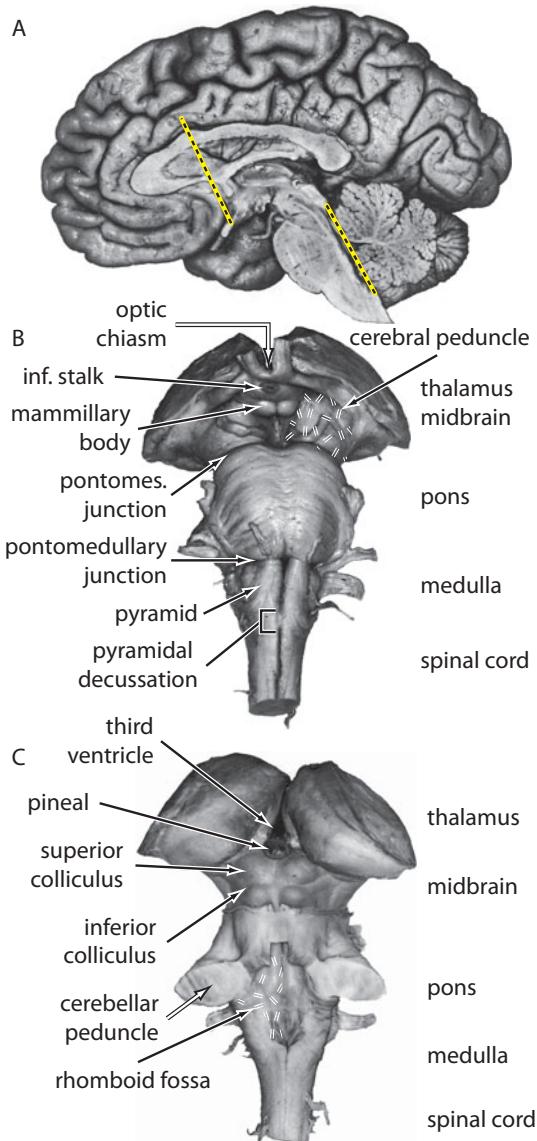
located deep within the brain! How is this possible? As the cerebral cortex expands caudally to cover the thalamus, midbrain, and part of the hindbrain, the expanded cerebral cortex is folded over a space that is outside of the brain. The boundaries of this region or cavity, termed the **velum interpositum**, are the corpus callosum on the dorsal side and the roof of the diencephalon and brainstem on the ventral side (Fig. 3-9). The velum interpositum does not contain CSF, and it houses large vessels including the **internal cerebral veins**, as well as the pineal gland. Most importantly for the purpose of this chapter, if you can visualize that the velum interpositum lies *outside of the meninges*, even though it is located deep within the brain, then you have conquered the most difficult part of forebrain anatomy. In this way, the velum interpositum serves as a great litmus test for understanding the three-dimensional anatomy of the forebrain.

THE CEREBRAL CORTEX COVERS MUCH OF MIDBRAIN AND THALAMUS

Very little of the brainstem or diencephalon is visible when viewing an adult human brain from the outside. This is because the expansive telencephalon and cerebellum overlie most of the brainstem and diencephalon. The cerebellum covers most of the dorsal surface of the medulla and the entire dorsal surface of the pons. In the human, the greatly expanded cerebral cortex covers all but small regions of the midbrain and diencephalon. Therefore, in order to see major landmarks and regional boundaries, the cerebral and cerebellar cortices must be dissected away from the brainstem and thalamus (Fig. 3-10A). This dissection is accomplished with just a pair of bilateral cuts. The **cerebellar peduncles** are white matter tracts that straddle the pons and connect the cerebellum to the rest of the brainstem. When the cerebellar peduncles are cut, the cerebellum can be removed, revealing the rhomboid fossa. To remove the telencephalon from atop the thalamus, diagonal cuts are made

Figure 3-10. A: The cerebral and cerebellar cortices obscure the brainstem and thalamus from view. Two diagonal cuts through the lamina terminalis (left dotted line) and bilateral cuts across the cerebellar peduncles (right dotted line) reveal the medulla, pons, midbrain, and thalamus. B: A view of the brainstem and diencephalon from the ventrum shows the pyramidal decussation that marks the border between the spinal cord and the medulla. In this view, the bulbous ventral pons is clearly demarcated. Caudally, the pons borders the medulla (pontomedullary junction) and rostrally, the pons abuts the mesencephalon (pontomes. junction). The cerebral peduncles (white hash marks) dominate the ventral midbrain. The mammillary bodies, infundibular stalk (*inf. stalk*) and optic chiasm are all present on the ventral surface of the diencephalon. C: A view of the brainstem and diencephalon from the dorsal side reveals the rhomboid fossa (white hash marks), which is occupied by the fourth ventricle. The cut cerebellar peduncles are visible. In the midbrain, the inferior colliculi and superior colliculi dominate the dorsal landscape. The thalamus is marked by the location of the pineal gland and the third ventricle.

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through the lamina terminalis. The result of these few cuts is a dissected pons, medulla, midbrain, and thalamus.

A FEW EXTERNAL LANDMARKS PROVIDE A BASIC NAVIGATIONAL FRAMEWORK TO THE BRAINSTEM AND THALAMUS

To enable the reader to recognize the different subcortical regions of the brain, we now consider the most prominent landmarks that mark each region. The spinal cord, medulla, pons, midbrain, and thalamus are lined up in succession,

a result of neural tube development. From the ventral side (Fig. 3-10B), the spinomedullary junction is marked by the **pyramidal decussation**. This **decussation**, or crossing, is the site where axons carrying signals necessary for voluntary movements cross the midline. Within the medulla, motor-related fibers travel in the **pyramids**, two parallel columns running down on either side of the ventral medullary midline. The pyramidal decussation is apparent, when viewing the brain from the ventral surface, as a blurring of the otherwise well-marked midline fissure.

The borders of the pons with both the medulla and the midbrain are marked clearly on the ventral side by the protrusion of the base of the pons or **basis pontis**. Two large tracts, the cerebral peduncles, are evident on the ventral surface of the midbrain. The ventral markers of thalamus include:

- The mammillary bodies are nuclei important to memory formation and are the major target of axons in the fornix.
- The **infundibular stalk**, or simply **infundibulum**, forms the attachment between the hypothalamus and the pituitary.
- The optic chiasm is a white matter commissure where some axons from the retina cross en route to the thalamus.

On the dorsal side (Fig. 3-10C), the rhomboid fossa that contains the fourth ventricle stands out prominently. The fourth ventricle covers the pons and rostral portion of the medulla. On either side of the rhomboid fossa are the cerebellar peduncles, the caudal edge of which forms the border between the medulla and pons. The dorsal midbrain is distinguished by four hills or **colliculi** (single form is **colliculus**). The caudal colliculi are called the **inferior colliculi** and comprise an important component of the auditory pathway. The rostral pair of colliculi, the **superior colliculi**, is important for producing orienting movements of both the eyes and body toward moving objects or unexpected sounds.

The thalamus is located just rostral to the superior colliculi. The pineal gland, a non-neural gland derived from neural tube, attaches to the caudal thalamus and extends caudally between the superior colliculi. The other notable external marker of the thalamus is the roof of the third ventricle. With just the dozen or so landmarks introduced here, the student can identify the medulla, pons, midbrain, and thalamus.

DEVELOPMENT CONTINUES POSTNATALLY

Development does not stop at birth. In fact, most of the neurons in the cerebellum are born during the first several years of human life. Axons are not fully myelinated until 2 or 3 years after birth. The number of synaptic connections peaks within the first year of life and then steadily declines. This synaptic pruning, possibly of unused or rarely used synapses, continues into the teenage years. More subtle changes than pruning also occur with adjustments of synaptic strength.

Thus, connections are made, honed, and pruned at a steady rate throughout childhood and adolescence.

Learning to use our brain, learning how to interpret the neural signals evoked by external and internal stimuli, and learning the effect of activity in our brain on our muscles, is a process that occupies our infancy and childhood. As will be discussed in later chapters, the ability to develop certain capabilities is optimal during the early years of life. For example, animals, including humans, need to *learn how to see*, meaning how to convert neural signals arriving from the retina into the recognition and interpretation of visual scenes. If a cat or a human or other mammal does not see early during its life, because of congenital cataracts, severe myopia, or the like, that animal will never see well. Even if perfect optics are restored to the individual during adulthood, the person will be unable to understand and interpret what he or she sees. The window of time when we must train our brain for vision occurs during early life. Missing that window means that vision will never be normal. Once adulthood is reached, the brain remains somewhat plastic although far less so than is the case during childhood. Beyond allowing adults to grow and change, learning in adults allows for partial recovery from brain injuries including strokes.



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SECTION 2: NEURAL COMMUNICATION

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CHAPTER 4

THE NEURON AT REST

Perception, action, thoughts, emotions all require active communication between neurons and between neurons and peripheral structures. In this section of five chapters, we examine electrical signalling, the predominant mode of neuronal communication. First, we cover the electrical properties of a single neuron, *at rest*, that provide the fundamental basis for receiving, integrating, and sending electrical messages. In Chapter 5, we focus on how a single neuron can integrate multiple electrical inputs and then communicate the result across an often long axonal distance by using an action potential. Chapter 6 describes how the release of packets of neurotransmitters is triggered, enabling one cell to send a chemical message to another cell. In Chapter 7, we consider how packets of neurotransmitters are formed and what happens to neurotransmitters after release. Finally, in Chapter 8, the effects of neurotransmitters on the receptors of target cells are described. This takes us full circle, from the electrical integration of inputs to sending an electrical message, and finally to receiving that electrical message. We will then use this fundamental knowledge to understand how neuronal circuits support behavioral and perceptual functions in future sections.

As the reader understands by now, neurons communicate with other cells and also between their own near and distant parts by using electrical signaling. Here, we describe the electrical properties of the neuron under *resting* conditions. When a neuron is at rest, meaning it is not firing an action potential, two features dominate the neuron's electrical landscape:

- The resting membrane potential
- Graded synaptic inputs

The **resting membrane potential** represents the default electrical potential (see Box 4-1 for review of electrical terms) of the neuron in the absence of any inputs. Neurons return again and again to this default, but critical, electrical potential. A failure of neurons to maintain an adequate resting membrane potential results in a complete disruption of function. The second influence on a neuron's membrane potential is synaptic input. In this chapter, we consider subthreshold synaptic inputs that cause graded responses but do not cause a neuron to fire an action potential.

ELECTRICAL TERMS ARE EASILY CONCEPTUALIZED BY CONSIDERING PLUMBING ANALOGIES.

The meaning of most electrical terms can be visualized using a water analogy. For those needing a brief reminder of fundamental principles and terms of electricity, consider the following analogies:

- **Electrical potential or voltage:** Water at the top of a tall waterfall can fall a long way and thus has a large amount of potential energy. Water on top of a short waterfall has a lower potential. Water in a land-locked lake has no potential and thus represents zero potential or the **ground** state. Note that electrical potential and voltage are synonymous.
- **Current:** The amount of water flowing past a point, in terms of volume per unit of time, represents the current.
- **Charge:** The integrated current over time is charge. In a water analogy, volume is therefore analogous to charge.
- **Resistance:** Narrower channels or pipes present greater resistance to water flow than do wider pipes. For this reason, firefighters use wide hoses rather than garden hoses to put out fires.

- **Conductance:** The inverse of resistance, conductance is higher in wide, unimpeded channels, such as a firefighter's hose, than in narrow pipes.
- **Capacitance:** There is no perfect water analogy for capacitance, which relates to how voltage changes over time. As a very rough approximation, consider that water in one lake must fill a bucket before entering a stream. The water will reach the stream *more slowly* if a large intermediary bucket must be filled than if a small one needs to be filled. Thus, the large bucket transfer system has a higher capacitance than does the small bucket one. Capacitance impacts the rate of charge transfer—or water transfer in this case—but does not change the eventual outcome: given enough time, all the lake water will make its way into the stream, regardless of whether it is transferred by a small or large bucket. Although this analogy fails under scrutiny, the important point to remember is that *voltage changes slowly across a high-capacitance membrane and rapidly across a low-capacitance membrane*.

MEMBRANES PREVENT THE FREE DIFFUSION OF CHARGED MOLECULES

As the biological version of a wall, *membranes* are absolutely necessary for life and indeed serve the fundamental role of defining the limits of an organism. Within living beings, membranes separate *cells*, the structural units of life. Membranes that surround cells, including neurons, termed **cellular** or **plasma membranes**, separate the inside of a cell, the **intracellular** compartment, from the outside or **extracellular** space.

Glycerophospholipids are the main constituents of biological membranes. Glycerophospholipids possess one **hydrophilic**, or water-friendly, head and two **hydrophobic**, or water-repelling, tails (Fig. 4-1A). In biological membranes, two layers

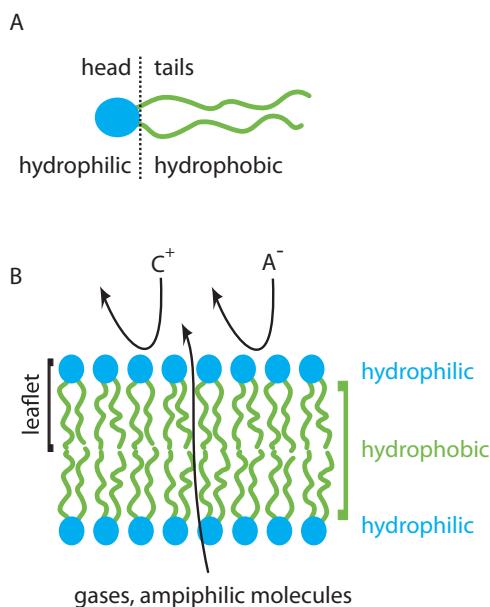
of lipids are arranged in a tail-to-tail fashion, termed a **bilayer**, with the hydrophobic tails intermingling (Fig. 4-1B). The hydrophilic heads of the lipids face either the extracellular space or the intracellular **cytosol**. The action of specific enzymes can alter the composition of the inner and outer **leaflets**, or layers, so that different lipids predominate in the inner leaflet, the one bordering the cytosol, and the outer leaflet that borders the extracellular space.

The hydrophobic core of biological membranes, formed by lipid tails, repels charged molecules. As a result, charged molecules cannot penetrate the tail region of the lipid bilayer and thus cannot cross the membrane (Fig. 4-1B). *The plasma membrane's hydrophobicity prevents the free diffusion of both large and small charged molecules*; the latter are termed **ions**. In contrast, gases and small amphiphilic substances, such as fats, cholesterol, and importantly most **general anesthetics**, diffuse freely through biological membranes.

Although charged molecules cannot move across lipid bilayers, they do move across biological membranes through several specialized routes that extend into both the extracellular and intracellular compartments. The routes are formed by **membrane proteins**, proteins that are anchored within the membrane and span the bilayer. Typically, multiple protein **subunits** complex together and extend across the lipid bilayer to provide routes through which ions can cross a lipid bilayer or membrane. Broadly speaking, there are three types of **transmembrane** or membrane-spanning protein complexes that allow for the movement of ions and/or large molecules across the membrane:

- Ion channels
- Transporters
- Gap junctions

Figure 4-1. A: The lipids that make up biological membranes, primarily glycerophospholipids, have a head that is hydrophilic and two tails that are hydrophobic. Two layers of tail-to-tail aligned lipids form a bilayer, so that a wide hydrophobic core is bounded on either side by shallow hydrophilic borders. B: Flipases and scramblases are membrane enzymes that move lipids between the two layers or leaflets of a biological membrane. As a result, the two leaflets of a plasma membrane typically contain somewhat different lipid compositions (not illustrated). Ultimately, membranes prevent the free diffusion of charged molecules, anions (A^-) and cations (C^+) while allowing gases and **amphiphilic** molecules, compounds that have both hydrophilic and hydrophobic regions, to freely move between the separated compartments.



When appropriate conditions occur, ion channels switch from a *closed conformation* to an *open conformation*. The open conformation of an ion channel forms a **pore** through which ions pass (Fig. 4-2A). The pore is typically *selective*, so that only a particular ion or set of ions, distinguished by size and/or charge, passes through. The formation of the pore is termed **opening** the channel. Channel opening is triggered or **gated** when the voltage difference across the membrane reaches a certain value, in the case of **voltage-gated channels**, or when a **ligand**, such as a neurotransmitter, binds to the channel in the case of **ligand-gated channels** (see more below and in Chapter 8).

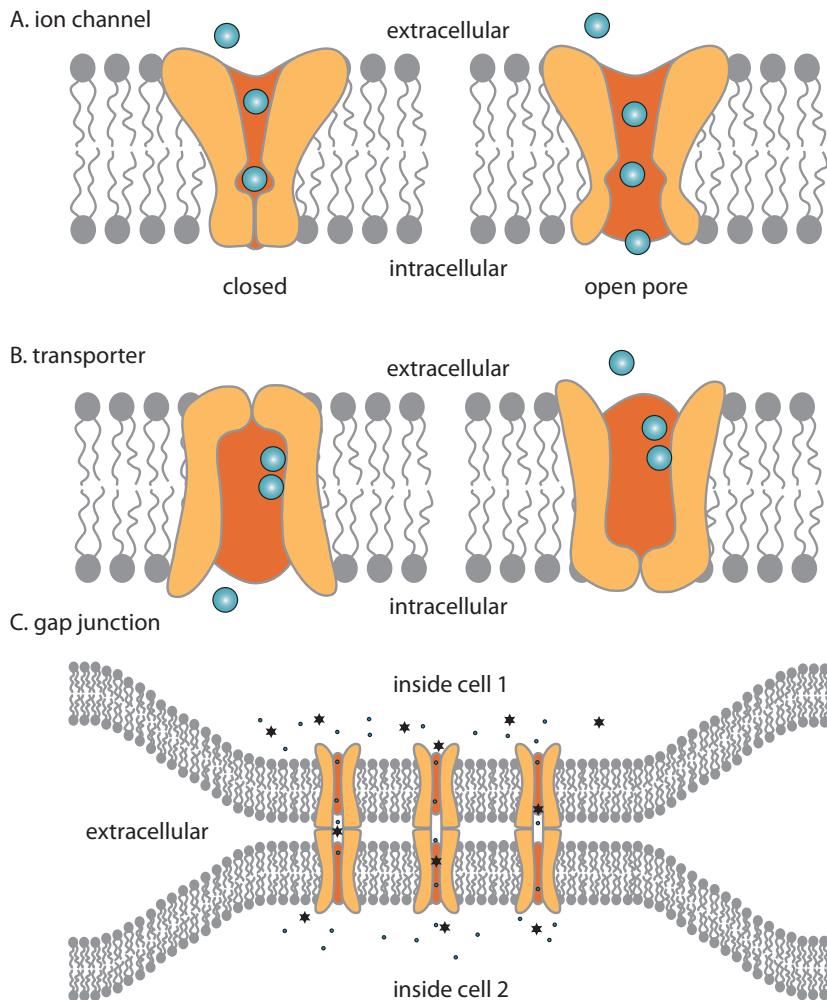


Figure 4-2. Charged molecules (blue spheres) only traverse biological membranes through specialized membrane-spanning proteins. An ion channel, a transporter, and a gap junction, three different types of membrane proteins, are shown in cross section. **A:** Ion channels can be either open or closed. In the closed configuration (left), ion channels do not allow ion movement across the membrane. In the open configuration (right), ion channels form a pore that allows ions to cross between the cytosol and the extracellular space. **B:** Transporters move ions and other small molecules across the membrane without ever forming a membrane-spanning pore. There are several different types of molecular transporters, only one of which is illustrated. **C:** Gap junctions form a conduit between the inside of two different cells (in this case cell 1 and cell 2) through which a variety of ions (small dots) and large molecules (larger black stars) can move. At the site of a gap junction, the membranes of the two cells involved are closely juxtaposed, being separated by about 3 nm rather than the normal intercellular separation of 30 nm or so. Complementary membrane proteins, termed **connexins**, in the two cells join to form an actual pore.

Transporters exist in many varieties, including **pumps** and **exchangers** or **carriers**, and use energy, from adenosine triphosphate (ATP) or from an existing electrochemical gradient, to move molecules across the membrane without forming a pore (Fig. 4-2B). Gap junctions are large pores *between cells* through which molecules below a certain size pass (Fig. 4-2C). Thus, unlike transporters and ion channels, *gap junctions traverse the extracellular space and two lipid bilayers, connecting the cytosol of two different cells*. In the nervous system, ions, metabolites, and signalling molecules all pass through gap junctions. A wide variety of molecules modulate gap junctions, allowing for functional modification of the molecules allowed across during different circumstances.

MECHANISMS UNDERLYING THE RESTING MEMBRANE POTENTIAL OF A NEURON DETERMINE EXCITABILITY

All cells have a resting membrane potential that stems from an uneven distribution of charged molecules across the plasma membrane. Yet, the mechanisms that maintain a neuron's resting membrane potential possess special significance because *the degree to which a neuron keeps its resting membrane potential, even in the face of inputs that result in deviations, determines that cell's excitability*. Cells that deviate easily from rest potential can reach the threshold for an action potential quickly and thus are highly excitable, whereas those that deviate briefly and rarely from rest, nearly always returning quickly to the resting membrane potential, are far less excitable. *Two neurons with the same rest potential, supported by different electrochemical mechanisms, are likely to differ in excitability.* For this reason, it is important to not only remember that the resting membrane potential of most neurons is -50 to -70 mV but also to understand the various electrochemical forces contributing to that rest potential.

INTRACELLULAR ORGANIC ANIONS ARE NOT PRESENT EXTRACELLULARLY

Like the rest potential of glial, epithelial, muscle, blood, and other types of cells, the potential of a neuron at rest is negative with respect to the extracellular fluid. One reason for the ubiquitous negative rest potential among living cells is that many of the molecules needed for life—nucleic acids, two amino acids, and many proteins—are negatively charged molecules, or **anions**, and most of these do not leave the cell (see Box 4-2). The large organic anions are too large to diffuse across the membrane, and specific mechanisms to transport most of these anions, excepting those that double as neurotransmitters (see Chapter 7), do not exist.

Box 4-2

A NUMBER OF ORGANIC ANIONS ARE INTEGRAL TO CELLULAR PHYSIOLOGY.

Molecules critical to life that carry negative charges include:

- Adenosine triphosphate (ATP) and adenosine diphosphate (ADP) with 3–5 negative charges per molecule
- Nucleic acids with a negative charge associated with the phosphate group of each nucleotide
- Aspartate and glutamate

Large nucleic acids do not leave the cell, and thus provide a major source of excess negative charge within living cells. Within the cytosol, nucleic acids such as tRNAs and mRNAs, as well as other organic anions complex with positively charged ions, typically Mg^{++} , so that the intracellular solution remains neutral. Although aspartate and glutamate serve as neurotransmitters in some neurons, they serve critical functions in all cells, including all neurons, and are present at substantial concentrations, in the millimolar range.

FOR ANY ION TO EXIST IN A STEADY STATE, ITS ELECTRICAL AND CHEMICAL GRADIENTS MUST BE EXACTLY AND OPPositely BALANCED

Three small ions move across the neuronal membrane at rest. These ions include two positively charged ions, or **cations**, potassium (K^+) and sodium (Na^+), and one small anion, chloride (Cl^-). Each of these ions is differentially distributed across the membrane of a neuron, with potassium ions more prevalent inside the cell and sodium and chloride ions more prevalent outside. When a cell is at rest, each ionic species exists in steady state, with the same number of ions leaving the cell as entering it. Before considering how all three ions arrive at steady state, we consider how just one ionic species, K^+ , reaches electrochemical equilibrium.

Potassium ions exist at a much higher concentration inside the mammalian neuron (155 mM) than outside (5 mM), so that a chemical driving force pushes potassium ions outward (Fig. 4-3). However, since neurons are negative with respect to ground, electric forces attract potassium ions inward. Thus, chemical and electrical driving forces oppose one another, with the electrical driving force pushing potassium ions to the negative side, which is the intracellular side of the membrane, and chemical forces pushing potassium ions to the extracellular side where the potassium ion concentration is lower.

At steady state, the chemical and electrical driving forces exerted on potassium ions are equal but opposite (Fig. 4-3). The electrical potential (E_x , see Box 4-3),

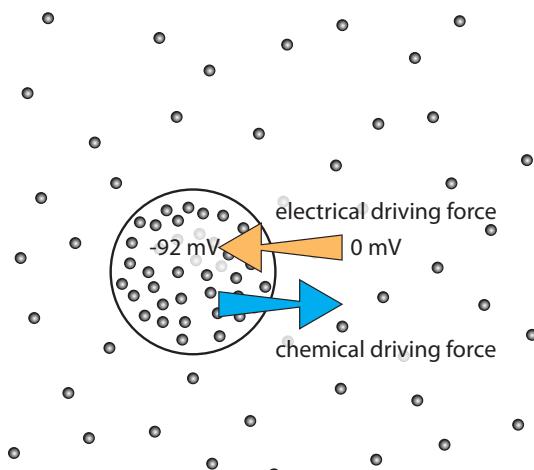


Figure 4-3. The steady-state potential, where there is no net flux of potassium ions (spheres), occurs at the potential where the chemical (outward arrow) and electrical (inward arrow) forces exerted on any given ionic species are equal and opposite. The potassium ion concentration inside cells is roughly 30-fold higher than that in the extracellular fluid. Therefore, chemical forces push potassium ions out. Since cells are negative with respect to ground, electrical forces push the positively charged potassium ions in. If we consider potassium ions exclusively, the steady state potential predicted by the Nernst equation is about -92 mV.

Box 4-3

ELECTRICAL POTENTIAL AND VOLTAGE ARE EQUIVALENT TERMS.

Electrical potential difference, symbolized by **E**, is the same as voltage, symbolized by **V**.

where the chemical and electrical forces on any given ionic species, X, are exactly opposing is given by the **Nernst equation**. By calculating the value of a term encompassing several constants at mammalian body temperature, the Nernst equation can be simplified to:

$$E_x = 62 * z * \log \frac{[X]_o}{[X]_i}$$

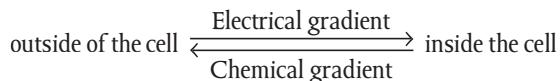
where $[X]_o$ and $[X]_i$ are the extracellular and cytosolic concentrations of the ionic species in question. The term z refers to the valence of the ionic species. For potassium ions and other monovalent cations, the valence is +1, and for monovalent anions, such as the chloride ion, $z = -1$. This brings us to an expression of the Nernst equation for potassium ions:

$$E_K = 62 * (+1) * \log \frac{[K]_o}{[K]_i}$$

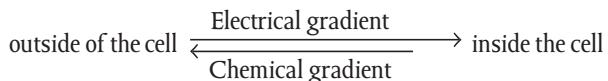
where $[K]_o$ and $[K]_i$ are the extracellular and intracellular concentrations of potassium ions. If we plug in physiological values for $[K]_o$ and $[K]_i$, 5 and 155 mM, respectively, we can solve the Nernst equation for potassium ions:

$$E_K = -92 \text{ mV}$$

Thus, when the neuron is at a potential of -92 mV with respect to the outside of the cell, the electrochemical gradient for potassium ions is at steady state, with the same number of potassium ions leaving as entering the cell.

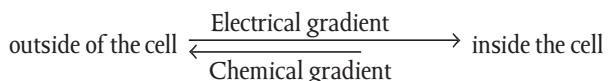


Furthermore, if an outside current perturbs the cell's membrane potential, taking it away from -92 mV , the cell will, in short order, return back to -92 mV . For example, if one injected negative current into a cell, so that the membrane potential reached -100 mV , the excess electrical gradient, opposed by an unchanged chemical gradient, would now *drive* potassium ions into the cell:



until the cell's membrane potential returned to the E_K value of -92 mV .

Now, consider the consequences of increasing the extracellular potassium ion concentration. Elevation of the extracellular potassium ion concentration, in either an experimental or pathological setting, has two consequences: (1) it decreases the chemical gradient, and (2) it increases the electrical gradient. Both of these changes result in more potassium ions entering than leaving the cell:



until a new steady state potential is reached. As above, more potassium ions would enter than leave the cell until the electrical and chemical gradients once again were exactly opposite. Remember that a higher-than-normal extracellular potassium ion concentration will change the Nernst potential for potassium ions, E_K , in this case to a more positive value than -92 mV. These examples highlight two important concepts:

- The **driving force** is proportional to the difference between the membrane potential (V_m) and the Nernst potential ($V_m - E_x$). In the case of potassium ions, the further away from E_K that the membrane potential deviates, the more driving force ($V_m - E_K$) exists to redistribute potassium ions until V_m returns to E_K .
- The **reversal potential** is the membrane potential, where the driving force equals zero. In our example, where we are only concerned with potassium ions, the reversal potential is E_K or -92 mV, the potential where $V_m - E_K = 0$. Above the reversal potential, potassium ions leave the cell, and below the reversal potential, the net flow of potassium ions reverses, so that potassium enters the cell. Thus, when the membrane potential is more polarized (from ground), or **hyperpolarized**, than -92 mV, potassium ions enter the cell, and when the membrane potential is less polarized, or **depolarized**, than -92 mV, potassium ions leave the cell.

The above gives a nearly accurate picture of the resting membrane potential in astrocytes and cardiac muscle cells, where potassium ions are the exclusive, or nearly so, ionic species that crosses the membrane at rest. Thus, the resting membrane potential of astrocytes and cardiac muscle cells is about -90 mV. However, as we shall see in the next section, by considering only potassium ions, we have greatly oversimplified the resting electrical properties of neurons.

THE RESTING MEMBRANE POTENTIAL DEPENDS ON THE DISTRIBUTION OF ALL IONS THAT PERMEATE THE MEMBRANE

Astrocytes contain ion channels that allow potassium ions to **permeate**, or pass through, the cellular membrane. Additional channels populate the astrocytic membrane but only potassium channels are open at resting membrane potentials. Therefore, only potassium ions contribute to the resting membrane potential of an astrocyte.

The situation is different in a typical neuron. In addition to channels permeable to potassium ions, channels permeable to sodium and chloride ions are also open at rest potential. Thus, the resting membrane potential, the default potential of a cell, depends on two factors:

- The ion species to which a neuronal membrane is permeable at rest. Permeability depends not only on the presence of ion channels through which

an ion can pass but also on the conformation of the ion channel. As an analogy, there may be many doors into a night club but if they are all locked and thus impermeable, then no one gains entrance.

- The concentrations of the permeant ions on the two sides of the membrane. Obviously if it is 8 a.m. and no one is waiting to get into the night club, it does not matter whether the doors are locked or open.

As mentioned above, three ionic species—potassium, chloride, and sodium—permeate neuronal membranes at rest. We already know that $E_K = -92$ mV. Given the distribution of chloride and sodium ions, we can calculate E_{Cl} and E_{Na} as follows:

$$E_{Cl} = 62 * (-1) * \log \frac{[Cl]_o}{[Cl]_i} = -62 * \log \frac{100}{7} = -71 \text{ mV}$$

and

$$E_{Na} = 62 * (+1) * \log \frac{[Na]_o}{[Na]_i} = 62 * \log \frac{145}{12} = 67 \text{ mV}$$

Clearly, neuronal resting membrane potentials of -50 to -70 mV must be more influenced by the negatively valued E_K and E_{Cl} than by the positively valued E_{Na} . To quantify this, we use the **Goldman-Hodgkin-Katz** (or **GHK**) equation to weight the contributions of each ion's equilibrium potential by the membrane's permeability for that ion. As with the Nernst equation, we simplify the GHK equation by calculating the constant terms at human body temperature:

$$V_m = 62 * \log \frac{(P_K * [K]_o + P_{Na} * [Na]_o + P_{Cl} * [Cl]_o)}{(P_K * [K]_i + P_{Na} * [Na]_i + P_{Cl} * [Cl]_i)}$$

where P_K , P_{Cl} , and P_{Na} are the relative permeabilities for each ion species in a neuron at rest. Like astrocytes, neurons are most permeable to potassium ions at rest. We set P_K to 1, and then express the permeabilities of sodium and chloride ions relative to P_K . In fact, P_{Na} and P_{Cl} vary from one neuron to another. The most definitively established resting permeabilities come from experiments using a very large axon found in the squid! For the squid giant axon, the permeabilities of potassium, chloride and sodium ions are:

$$P_K = 1.00$$

$$P_{Cl} = 0.45$$

$$P_{Na} = 0.04$$

The relative permeabilities of chloride and sodium ions in mammalian neurons are likely to be close to these values. Another way to view this is that potassium ions carry 60%–70% of the current in a typical resting neuron, chloride ions carry 25%–35%, and sodium ions carry only about 3%–4% of the current.

If we use ion permeabilities from the squid giant axon along with ion concentrations observed in mammalian neurons, we can use the GHK equation to calculate the resting membrane potential as:

$$V_m = 62 \cdot \log \frac{((1) \cdot (5) + (0.04) \cdot (145) + (0.45) \cdot (7))}{((1) \cdot (155) + (0.04) \cdot (12) + (0.45) \cdot (100))}$$

$$= 62 \cdot \log \frac{(5+6+3)}{(155+0+45)}$$

$$= -72 \text{ mV}$$

Box 4-4

ELEVATIONS OF THE EXTRACELLULAR POTASSIUM ION CONCENTRATION DEPOLARIZE THE RESTING MEMBRANE POTENTIAL.

Hyperkalemia, an elevated potassium ion concentration in the blood, and thus in extracellular fluid, can be caused by kidney failure, by certain congenital conditions, and by a number of drugs. Regardless of the etiology, elevated potassium ion levels outside of the cell will decrease the chemical gradient for potassium ions. For example, if $[K]_o$ were raised from a normal value of 5 mM (range of normal values is 3.5–5.0 mM) to 7 mM, the new Nernst potential for K^+ would be -83 mV, and the new Goldman-Hodgkin-Katz (GHK) equation-prediction for the resting membrane potential would be more positive by several millivolts. In other words, typical neurons would depolarize by 5 or so millivolts. The cells most affected by hyperkalemia are cells with resting membrane potentials most dominated by potassium ions. Glial astrocytes are one such cell type, but of more clinical concern are cardiac muscle cells. Depolarization of cardiac muscle can be fatal for reasons that will become clear in the next chapter, after we describe the action potential.

The GHK equation quantifies the reality that *the equilibrium potential of any ionic species only influences a cell's membrane potential to the extent that the cell is permeant to that ionic species*. The number, selectivity, and conformational state of ion channels limit the movement of ions across the cell membrane just as the number, type, and state of doors limit access to a room. A cat door lets cats in and out but not large dogs or people. Organic anions, although at grossly different concentrations on either side of the membrane, do not contribute to the resting membrane potential because they cannot cross neuronal membranes. Sodium ions contribute only a little to the resting membrane potential because they have low permeability at the negative potentials of neurons at rest. In contrast, potassium ions contribute the most to the resting membrane potential because of the high permeability to potassium at rest (see Box 4-4).

Relative ion permeabilities, with P_K greater than P_{Cl^-} , which in turn is far greater than P_{Na^+} , are the same in human neurons as in the well-studied squid axon. Yet, the absolute ion permeabilities of a squid axon are bound to be inaccurate for many, perhaps even most, mammalian neurons. What consequence would changes in P_{Cl^-} or P_{Na^+} make for the rest potential calculated from the GHK equation?

- Since the calculated rest potential, -72 mV, is so close to our calculated E_{Cl^-} of -71 mV, changing P_{Cl^-} will not change the GHK equation-calculated rest potential. This holds as long as chloride ions are far more concentrated outside than inside the cell, a condition which is itself modified in many circumstances (see below).
- Even small changes in the relative resting permeability to sodium ions can substantially alter the calculated rest potential. This conclusion follows from the large difference between the positively valued E_{Na^+} and the negative rest potential.

In truth, the rest potential of mammalian neurons varies from about -70 mV, close to our calculated value, to about -50 mV. A rest potential substantially more depolarized than our GHK equation-calculated potential can result either from additional minor permeabilities, for example to calcium ions or from changes in the chloride ion distribution across the membrane.

DIFFERENT CHLORIDE TRANSPORT MECHANISMS PRODUCE DIFFERENT DISTRIBUTIONS OF CHLORIDE IONS

The distribution of chloride ions is actively determined by transporters that shuttle chloride ions across the membrane. Two types of chloride transporters exist:

- A sodium / potassium /chloride carrier, **NKCC**, transports chloride ions *into* the cell.
- A potassium /chloride carrier, **KCC**, transports chloride ions *out* of the cell.

In the absence of the KCC transporters, the internal concentration of chloride ions would be greater. As a result of a shallower chloride ion concentration gradient, the Nernst potential for chloride ions, E_{Cl} , would be more positive. It does not take much intracellular accumulation of chloride ions to raise E_{Cl} above the rest potential and thereby for chloride ions to leave the cell at rest. The departure of negatively charged chloride ions from the cell depolarizes the membrane potential.

THE VOLTAGE DROP ACROSS A MEMBRANE AT REST DEPENDS ON THE HIGH CAPACITY OF NEURONAL MEMBRANES TO HOLD CHARGE

The bulk, meaning free, solutions within the cytosol of a spherical cell and within the surrounding extracellular space are **isopotential** (Fig. 4-4). This means that there is no difference in the potential in one region of the cell relative to another. Similarly, there is no difference in the potential in different areas of the extracellular expanse. Instead, the membrane potential is maintained by an excess of negative charges nestled among and just inside the lipid heads of the inner leaflet and an excess of positive charges placed similarly on the outer leaflet of the membrane (Fig. 4-4). Beyond the immediate vicinity of the membrane, negative charges are neutralized by neighboring positive charges.

The resting membrane potential of a neuron, -50 to -70 mV, may appear to be an inconsequential voltage as it is only a tiny fraction of what is readily available in the wall outlets ubiquitous to modern societies or even in the small batteries that run common household devices. However, the voltage drop across neuronal membranes is maintained across the tiniest of distances. The numbers are astonishing. A 50 mV differential in electrical potential across about 5 nm, the approximate width of a lipid bilayer, is equivalent to a drop of 10,000 V across only one mm. The powerful charge separation exhibited by neuronal membranes results in a very high membrane **capacitance** (see more in Chapter 5).

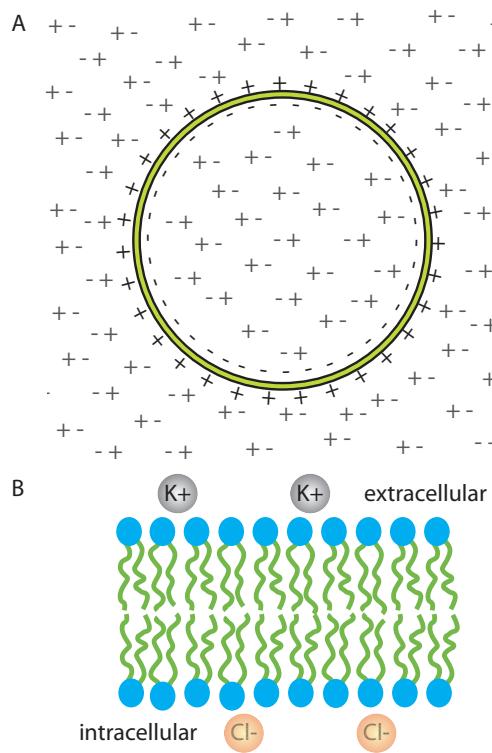


Figure 4-4. The bulk fluids inside and outside the cell are isopotential, meaning that near to every charged molecule is another molecule or molecules of equal but opposite charge. Yet, a potential difference exists across biological membranes. This potential difference across the membrane of a neuron is carried by extracellular cations, mostly potassium ions, and intracellular anions, mostly chloride ions, that sit in very close proximity to the membrane. **A** shows an overall view of a cell and the immediate extracellular environment, whereas **B** shows a magnified view of a short stretch of membrane.

NEURONS USE ACTIVE TRANSPORT TO PREVENT REDISTRIBUTION OF SODIUM AND POTASSIUM IONS

The movement of only about 1/100th of 1% of all the free ions in the cell are needed to maintain the resting membrane potential of a typical neuron. Yet, over extended time, if ions followed their electrochemical gradients, the intracellular concentration of potassium ions would decrease and the intracellular concentration of sodium ions would increase. To counteract these changes, the cell continuously, and at considerable cost, pumps out sodium ions while pumping in potassium ions. The Na^+/K^+ ATPase is a pump, a type of ion transporter that requires the hydrolysis of one ATP molecule in order to pump three sodium ions out and two potassium ions in (see Box 4-5). Because more sodium ions leave the cell than potassium ions enter, the Na^+/K^+ ATPase is **electrogenic**, meaning that it generates a current, in this case an **outward current**, or net positive movement to the extracellular side of the cell (Fig. 4-5). The outward current resulting from the Na^+/K^+ pump hyperpolarizes the resting membrane potential by roughly 5 mV in a typical neuron.

Box 4-5

DRUGS THAT BLOCK THE ATPASE PUMP CAN BE LETHAL.

Ouabain and **digitalis**, also called **digoxin**, are molecules that block the Na⁺/K⁺ ATPase pump. Blocking the pump is toxic, and at sufficient doses, both ouabain and digitalis are lethal. The initial result of blocking Na⁺/K⁺ transport is a depolarization of cellular membrane potentials. For reasons that will become clear in Chapter 5, depolarization of cardiac muscle cells leads to paralysis and **asystole**, or cardiac silence, and thus to death. When its dose is carefully titrated, digitalis can be used to regulate irregular heartbeats. The reasons why depolarization leads to paralysis and asystole will become evident in the next chapter.

SYNAPTIC INPUTS AFFECT NEURONS THROUGH SYNAPTIC CURRENTS AND CHANGES IN MEMBRANE RESISTANCE

The resting membrane potential is, of course, more a concept than a reality. Even the least active neurons do not maintain a flat-line membrane potential. Neurons in the central nervous system are constantly bombarded with synaptic inputs that alter their electrochemical gradients away from steady state. Furthermore, the exact complement of channels possessed by each neuron will tweak the final value of the resting membrane potential.

The electrical currents consequent to synaptic inputs are mediated by either the opening or closing of ion channels. By altering the conformation of ion channels, synaptic inputs generate **synaptic currents**. Synaptic inputs that result in the closing or opening of channels also alter the **input resistance**, or total resistance across the membrane, of a neuron. Thus, synaptic inputs can have either or both of two effects on neurons:

- A synaptic input may change the ionic current or **flux** that flows across the membrane. An **inward current** or net positive movement to the inside of the cell will depolarize a neuron and an outward current will hyperpolarize a neuron (Fig. 4-5).
- A synaptic input may change the input resistance.

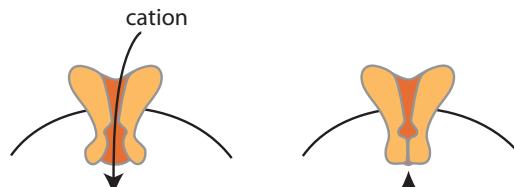
To understand how synaptic currents and changes in input resistance affect the membrane potential of a neuron, we recall **Ohm's Law** from basic physics:

$$V = I \cdot R$$

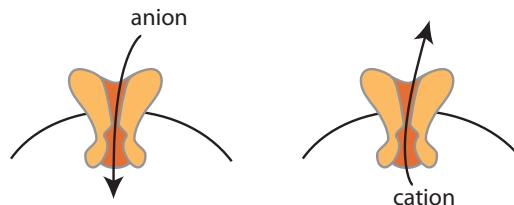
where V is voltage, I is current, and R is resistance. In the case of a neuron responding to a synaptic input, the change in voltage (V) elicited by a synaptic

Figure 4-5. A: Inward currents make the inside of the cell more positive. Most typically, they arise from a net influx of cations, typically sodium and/or calcium ions or from a reduction (red X) in the efflux of a cation, typically potassium ions. B: Most outward currents, which make the inside of the cell more negative, arise from the influx of anions, typically chloride ions or the efflux of cations, typically potassium ions.

A. Inward current



B. Outward current



input will equal the synaptic current (I) multiplied by the input resistance (R). Thus, a synaptic current is less effective in changing membrane potential when membrane resistance is low. Conversely, when membrane resistance is increased, as occurs when channels close, a synaptic current is more effective in changing membrane potential. As a consequence, one must know whether input resistance increases or decreases, as well as knowing whether the input elicits an inward or outward current, in order to predict the effect of a given synaptic input. Consider the consequences of closing potassium channels open at rest:

- An inward current
- An increase in input resistance

The inward current results from a decrease in the outward flux of positively charged potassium ions, which will have the effect of accumulating positive charges inside the cell and thus depolarizing the cell. The increase in input resistance follows simply from the *closing* of the potassium channels. Together, the increase in input resistance and the inward current powerfully depolarize a cell and make it more excitable as well.

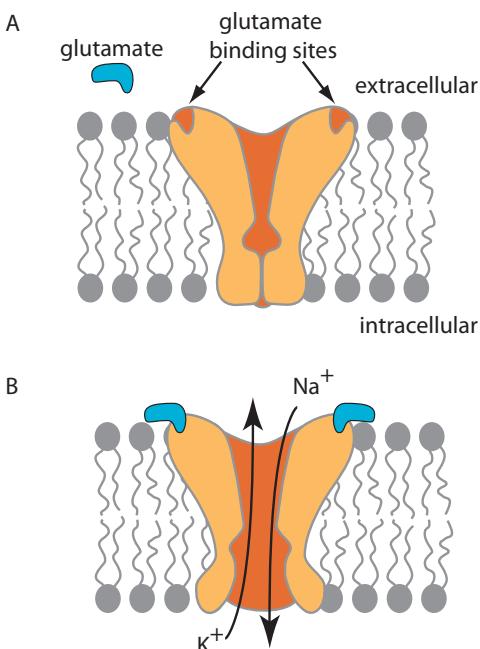
Broadly speaking, we can divide inputs from chemical synapses into two categories:

- **Excitatory synaptic inputs** make it more likely that a neuron will fire an action potential. These inputs typically elicit an inward current that depolarizes the neuron. Although excitatory inputs that cause an inward current through an increase in cation influx necessarily decrease input resistance, as a result of opening the cation channels, the excitatory effect of the inward current outweighs the inhibitory effect of the drop in resistance.
- **Inhibitory synaptic inputs** make it less likely that a neuron will fire an action potential. Inputs that elicit an outward current and/or decrease the cell's input resistance make a neuron less likely to fire an action potential.

The most prevalent type of excitatory synaptic input causes a large inward current that takes the cell toward the action potential threshold. The most prevalent inhibitory synaptic input results in the opening of a chloride channel. Since E_{Cl} is often more hyperpolarized than the rest potential, chloride ions flow into the cell, causing an outward current (remember that currents are named in the direction of net positive charge movement, Fig. 4-5). In addition, the open chloride channels reduce the cell's input resistance. The outward current and decreased input resistance combine to keep the cell hyperpolarized, far from the threshold for an action potential, and in a “leaky” state or state of low resistance that will make it harder to reach threshold.

Channels that open after binding directly to a neurotransmitter are **ionotropic receptors**. In other words, *an ionotropic receptor is both a receptor and a channel* (Fig. 4-6). In the next section, we consider how current through two such ligand-gated ion channels changes the membrane potential of a neuron initially at rest (see Box 4-6). Note that a *ligand-gated ion channel is the same thing as an ionotropic receptor*; the two terms are synonymous, simply different ways to refer to the same physical entity (Chapter 8).

Figure 4-6. Ionotropic receptors, such as the glutamate receptor shown here, possess a pore region through which ions can travel. Ionotropic receptors are a class of ligand-gated channels where a ligand, in this case glutamate, binds directly to the channel and *gates* a pore. In the absence of glutamate, the pore is shut (A). When two glutamate molecules bind to the two glutamate binding sites, the pore opens, allowing both potassium and sodium ions to pass (B).



WHEN AGONISTS BIND TO LIGAND-GATED IONOTROPIC RECEPTORS, IONIC PERMEABILITIES CHANGE

In physical terms, ligand-gated channels are transmembrane protein complexes that contain a neurotransmitter-binding region linked by three-dimensional structure or **conformation** to a pore region that can open or close and through which ions flow when open (Fig. 4-6). Typically, the ligand-binding site sits on the

Box 4-6

A LIGAND IS A MOLECULE THAT BINDS TO A RECEPTOR.

Ligands are molecules that bind to receptors just as keys fit into locks. A ligand that changes the activity of a receptor is called an **agonist**. In contrast, when **antagonists** bind to a receptor, they decrease either agonist binding or the effect of agonist binding without directly changing the receptor's activity. There are two major types of antagonists:

- **Competitive antagonists** bind to the same site as agonists do and thus directly compete for the binding site.

- **Noncompetitive antagonists** bind to a different site than do agonists and alter the conformation of the receptor to decrease either agonist binding or the effect of agonist binding.

Some ligands have intermediate or mixed effects. For example, a molecule that binds inefficiently to the agonist binding site can weakly activate the receptor as an agonist would, while also functioning as a competitive antagonist by denying other agonists access to the binding site.

outside of the transmembrane protein. The binding of a neurotransmitter causes the membrane protein to undergo a conformational shift that opens the pore running through the membrane. These pores are selective for certain ions that travel down their electrochemical gradients.

We focus here on the two most common ligand-gated channels in the central nervous system: a glutamate receptor called the α -amino- γ -hydroxyl-5-methyl-4-isoxazolepropionic acid (**AMPA**) receptor (after a particularly selective receptor **agonist**, see Chapter 8) and a γ -aminobutyric acid (**GABA**) receptor, the **GABA_A** receptor:

- The AMPA receptor is an ionotropic receptor that binds glutamate and opens a pore that allows both sodium and potassium ions to pass through (Fig. 4-6B).
- The GABA_A receptor is an ionotropic receptor that binds GABA, resulting in an open pore that selectively passes chloride ions.

In order to understand the effects of AMPA and GABA_A receptor activation, we use the same concepts introduced above to understand the resting membrane potential. *The voltage achieved after transmitter binding depends on the selective permeabilities and consequent reversal potential of the ligand-gated channels opened and on the driving force.*

WHEN GLUTAMATE BINDS THE AMPA RECEPTOR IN THE BRAIN, A PORE OPENS THAT ALLOWS BOTH SODIUM AND POTASSIUM IONS TO PASS

When open, the AMPA receptor is permeant to the two monovalent cations sodium and potassium, with the permeabilities of the two ions nearly equal, so that the AMPA receptor's reversal potential is about zero. Thus, when glutamate binds the AMPA receptor, sodium ions enter the cell and potassium ions exit the cell through the pore region of the receptor (Fig. 4-6B). For a cell sitting near the rest potential, -50 to -70 mV, the driving force will cause a net inward current. Therefore, the postsynaptic cell depolarizes. This depolarization is called an **excitatory postsynaptic potential** or **EPSP**. Although a unitary AMPA receptor-mediated EPSP may be quite small, many such EPSPs **summate** to reach threshold and trigger an action potential, thus *exciting* the cell (see Chapter 5).

Glutamate opens the AMPA receptor only *briefly*. The glutamate concentration in the synaptic cleft is reduced rapidly by effective reuptake (much more on this in Chapter 7). In addition, the AMPA receptor, like most ionotropic receptors, **desensitizes**. This means that the AMPA receptor enters a desensitized state in which no ion flux occurs even though glutamate is still bound to the receptor. Consequently, the effect of glutamate on a postsynaptic cell with AMPA receptors is transient, a quick depolarization followed by a return to the resting membrane potential. Since some

degree of desensitization marks all ionotropic receptors, postsynaptic potentials mediated by ionotropic receptors are *fast*, beginning and ending rapidly.

ACTIVATION OF GABA_A RECEPTORS OPENS A CHLORIDE CHANNEL

Now, consider the consequences that follow GABA's binding to its ionotropic receptor, the GABA_A receptor. The GABA_A receptor is a chloride channel, meaning that it is permeable to chloride ions. Yet, because E_{Cl^-} , calculated above as -71 mV, is so close to the resting membrane potential that we calculated for a typical neuron, -72 mV, the actual driving force is negligible. As a consequence, the absolute magnitude of the synaptic current, and consequently the change in voltage, elicited by GABA_A receptor activation can be small to nonexistent, particularly for neurons with membrane potentials near -70 mV. For neurons with a rest potential closer to -50 mV, GABA_A receptor activation causes an outward current that results in a small hyperpolarization toward E_{Cl^-} .

Relative to the small outward current that flows through GABA_A receptors in a neuron near the rest potential, the increased permeability to chloride ions and consequent decrease in input resistance often have a greater influence on the cell. The flux of chloride ions through GABA_A receptors reduces input resistance of the membrane. As a result, EPSPs such as those caused by glutamate's binding to AMPA receptors will be smaller—remember that $V = I^*R$, so that a reduction in input resistance (R) will result in a reduction in the membrane voltage change (V) evoked by a given synaptic current (I)—in a neuron with open GABA_A receptors. In essence, *the high permeability to chloride ions through GABA_A receptors serves to clamp a neuron at E_{Cl^-} near the rest potential and make that cell difficult to depolarize*. For this reason, neurons receiving many active GABA_A inputs are far less easily brought to action potential threshold than are neurons with few active GABA_A inputs. Thus, the net effect of GABA_A receptor-mediated inputs is inhibitory, and the resulting potential is termed an **inhibitory postsynaptic potential** or **IPSP**.

Since the GABA_A receptor causes both an outward current and a decrease in membrane resistance, this receptor is very effective in lowering excitability:

- The outward current causes a hyperpolarization that takes a neuron farther from the threshold for an action potential, so that the neuron requires more additional excitatory input to reach threshold than does a more depolarized cell.
- The decrease in input resistance decreases the voltage change evoked by any given synaptic current, so that a neuron needs more EPSPs to reach threshold and is therefore less excitable.

Because of the strong inhibitory effect of the ubiquitous GABA_A receptors, a number of important drugs—sedatives, sleep aids, and general anesthetics—act

Box 4-7

MODERN PHARMACEUTICALS INCLUDE MANY DRUGS THAT FACILITATE GABA_A RECEPTOR-MEDIATED TRANSMISSION.

Drugs that act on GABA_A receptors comprise a pharmaceutical treasure trove. In addition to a site where γ -aminobutyric acid (GABA) binds, GABA_A receptors contain sites where general anesthetics and **benzodiazepines**, which include **anxiolytics**, drugs that decrease anxiety, and **hypnotics**, drugs that promote sleep, and perhaps even alcohol bind. These sites facilitate the opening of the GABA_A receptor's chloride channel.

CHANGES IN THE ACTIVITY OR EXPRESSION OF CHLORIDE TRANSPORTERS CAN CHANGE EXCITABILITY BY ALTERING THE EFFECT OF GABA_A RECEPTOR-MEDIATED TRANSMISSION.

Recall that KCC is a potassium /chloride carrier that transports chloride ions *out* of the cell so that in the absence of KCC, E_{Cl} has a more positive value. Neonates do not express KCC transporters. Thus, during neonatal development, γ -aminobutyric acid (GABA), which opens a chloride channel, elicits an excitatory depolarization. GABA receptor-mediated excitation of neurons appears to play an important

role in correctly wiring up the nervous system. Then, during normal development, KCC transporter expression is upregulated and GABA elicits inhibitory effects. KCC dysfunction in the adult contributes to at least some cases of **temporal lobe epilepsy**, a disorder marked by the abnormally high excitability of cortical neurons in the temporal lobe.

on the GABA_A receptor to reduce the general excitability of the central nervous system (see Box 4-7).

Recall that the distribution of chloride ions is set up by the activity of chloride transporters, NKCC and KCC. If KCC, which transports chloride ions out of the cell, is less active, chloride ions accumulate intracellularly. It does not take much intracellular accumulation of chloride ions to raise E_{Cl} above the rest potential, so that chloride ions leave the cell at rest as well as in response to GABA signaling. When E_{Cl} increases to a potential more depolarized than the rest potential, there will be an efflux of chloride ions, an inward current, which will cause a depolarization. Excitability is then greatly increased, principally because the brake normally supplied by GABA_A receptor-mediated inhibition is disabled. The major inhibitory signal in the brain, GABA, now depolarizes rather than hyperpolarizes neurons. It should not be surprising then that a genetic defect in the KCC transporter is at the root of a rare form of human **epilepsy**, the quintessential disease of hyperexcitability (see Box 4-8).



ADDITIONAL READINGS

- Ben-Ari, Y. Excitatory actions of GABA during development: The nature of the nurture. *Nat Rev Neurosci* 3: 728–739, 2002.
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CHAPTER 5

ELECTRICAL COMMUNICATION WITHIN A NEURON

Neurons continually receive information, in the form of synaptic currents, and with the arrival of each new input, the neuronal membrane potential can change. As discussed in the last chapter, the voltage change resulting from each synaptic input is the product of the synaptic current and the membrane resistance. In this chapter, we examine how neurons integrate incoming synaptic inputs and communicate the resulting integral to the synaptic terminal. Although the mechanisms of postsynaptic potential (PSP) integration are common to all neurons, the mode of transferring that information to the synaptic terminal differs in different cell types. Some compact neurons and most neuroepithelial sensory cells that lack an axon do not use an action potential to transfer electrical signals within the cell. However, the majority of neurons are long enough to require an axon, a specialized neuronal process, to physically reach their targets. For these cells, action potentials provide a mechanism of communication that can travel the length of the axon to the synaptic terminal. Therefore this chapter focuses on three subjects:

- The integration of PSPs received over time anywhere on the surface of a neuron
- The transformation of excitatory information sufficient to reach threshold and produce an action potential and a full consideration of threshold
- The conduction of action potentials along axons, both unmyelinated and myelinated

Upon reaching the threshold for an action potential, a membrane depolarization is greatly amplified, increasing by tens of millivolts in a millisecond or so (see below). Thus, the action potential is said to depend on *active* currents. In contrast, graded potentials are integrated without any amplification. Because of this key difference, physiological processes that do not depend on an action potential are termed **passive**. Thus, the spatial and temporal integration of synaptic potentials and the resting membrane potential (see Chapter 4) are dependent on a neuron's **passive properties**.

THE POSTSYNAPTIC POTENTIAL THAT RESULTS FROM AN INPUT DEPENDS ON THE RECEPTOR INVOLVED AND THE PAST HISTORY OF THE NEURON

In the last chapter, we considered two common types of synaptic inputs:

- An **excitatory postsynaptic potential** (EPSP) mediated by an AMPA receptor
- An **inhibitory postsynaptic potential** (IPSP) mediated by a GABA_A receptor

The AMPA receptor–mediated EPSP and the GABA_A receptor–mediated IPSP are both fast potentials, deviating from and then returning to the rest potential all within milliseconds (Fig. 5-1A). Yet, PSPs come in nearly infinite variety as they differ in magnitude, latency to onset, time course of rise, and time course of decay. The variety in PSPs stems from two factors:

- The large number, more than a thousand, of different receptor types: different receptor types open or close a different channel or set of channels, doing so either directly and thus rapidly in the case of **ionotropic receptors**, or indirectly and therefore more slowly in the case of **metabotropic receptors** (Fig. 5-1B and see Chapter 8).

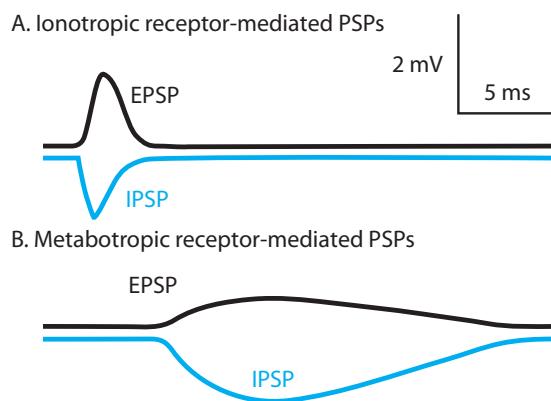


Figure 5-1. Postsynaptic potentials (PSPs) mediated by ionotropic receptors, such as the AMPA receptor for glutamate and the GABA_A receptor for GABA, reach their peak potentials rapidly and also return to baseline rapidly (A). In contrast to these fast postsynaptic potentials, slow postsynaptic potentials mediated by metabotropic receptors, such as the GABA_B receptor, have a delayed onset and can last for hundreds of milliseconds or even seconds or minutes (B). When a ligand binds to a metabotropic receptor, a series of intracellular reactions may eventually result in the opening or closing of ion channels and consequently a change in membrane potential. The magnitude of postsynaptic potentials, mediated by either receptor type, varies widely and only representative examples are shown here. The time course of metabotropic receptor-mediated postsynaptic potentials also varies a great deal; relatively short metabotropic receptor-mediated postsynaptic potentials are illustrated here.

- The past electrical history of a neuron: The history of electrical inputs to a cell confers a unique state of excitability to the cell.

Since synaptic voltage is the product of synaptic current and input resistance, recent or simultaneous synaptic inputs that change input resistance will also change the voltage response to a subsequent synaptic input. The voltage resulting from a synaptic current will be larger if input resistance is greater, due to closed channels, and smaller if input resistance is reduced, as occurs when ion channels open. For example, any input received during a long-lasting, conductance-increasing IPSP will cause less of a voltage change than if it arrived during a period of rest. Thus, the influence of any single input upon the membrane potential of a neuron is strongly colored by recent and synchronous inputs.

Synaptic inputs to a neuron arrive at widespread sites on the neuronal membrane, and they arrive at different times. If we consider a single site within a neuron, the influence of distant inputs, as well as past potentials, depends on how membrane potential changes across space and time, the topics considered in the following sections.

NEURONS SUMMATE POSTSYNAPTIC POTENTIALS ACROSS BOTH TIME AND SPACE

Most neurons in the human central nervous system receive at least hundreds and typically thousands of synaptic inputs. At any one moment, dozens of the synapses impinging on a neuron may release neurotransmitter causing PSPs. Postsynaptic potentials occurring at the same time summate over the entire cell surface, a process known as **spatial summation**. Postsynaptic potentials occurring at one place summate across time, a process known as **temporal summation**. Neurons continually summate inputs across time and space, employing spatial and temporal summation concurrently.

A LONG LENGTH CONSTANT ALLOWS POTENTIALS FROM WIDESPREAD REGIONS OF A NEURON TO EFFECTIVELY SUMMATE

To understand spatial and temporal summation, we need to understand how voltage changes across space and time, respectively. The term **length constant**, symbolized by the Greek letter lambda, λ , quantifies how a potential change decays as it travels down a cellular process (see Box 5-1). Lambda is the length that a potential travels down a cylindrical structure, such as a dendrite or axon, before it is reduced to 37%, or $1/e$, of its initial magnitude. If an EPSP has an

Box 5-1

THE NEURONAL LENGTH CONSTANT IS A MEASURE OF HOW MUCH A POTENTIAL CHANGE DIMINISHES AS IT TRAVELS.

To understand the length constant, we can use the water analogy that we used previously (see Box 4-1). Consider injecting 1,000 mL of water at one point along a pipe (Fig. 5-2). If the pipe walls are very leaky, the injected water will leak out and will not get very far, so that before too long, only 370 mL, or 37%, remain; this is an example of a short length constant (Fig. 5-2B). If the pipe diameter is thin, axial resistance will be very high and water will encounter so much resistance that it will not travel far, and again the length constant will be short (Fig. 5-2C). However, if the pipe diameter is wide with impermeable walls, injected water will travel a long distance, and the length constant will be long (Fig. 5-2D).

initial amplitude of 100 μ V, then after one length constant down the neuronal process, that same EPSP will have a peak amplitude of 37 μ V (Fig. 5-2A). The length constant is dependent on only two parameters:

$$\lambda = \sqrt{\frac{r_m}{r_a}}$$

where r_m is the membrane resistance and r_a is the axial resistance. Membrane resistance is a familiar concept by now; axial resistance is simply the resistance encountered as current travels down the inside of a process, either an axon or a dendrite. Axial resistance is greatest in the thinnest of neuronal processes and lowest in fibers with the largest diameter. The formula for the length constant essentially tells us that PSPs spread further as the membrane resistance increases and/or as the axial resistance decreases (Fig. 5-2B-D). Therefore, the largest values of length constant, some number of millimeters, are found in wide-diameter processes with a large r_m and small r_a ; as detailed below, large-diameter myelinated axons fit this bill. The smallest length constant values, a fraction of a millimeter, are found in the thinnest axons; unmyelinated axons fit this bill.

In sum, potentials travel the farthest with the least degradation in neurons with the greatest length constants. Therefore, *neurons with long length constants summate potentials arriving at widely dispersed sites. In contrast, neurons with short length constants are only affected by nearby synaptic potentials.*

A LONG TIME CONSTANT ALLOWS NEURONS TO EFFECTIVELY SUMMARIZE POTENTIALS ARRIVING OVER A LARGE RANGE OF TIME

The **time constant**, typically symbolized by the Greek letter tau, τ , is the time that it takes a potential to rise to 63%, or $1 - (1/e)$, of its final, steady state magnitude. Using the same example as above of an EPSP with a final amplitude of 100 μ V, the membrane will be depolarized by 63 μ V after one time constant has passed (Fig. 5-3). Like the length constant, the time constant is dependent on r_m , but it is also dependent on membrane capacitance or c_m :

$$\tau = r_m * c_m$$

As with the length constant, the time constant increases as membrane resistance increases. In addition, the time constant increases as capacitance, a measure of a membrane's ability to store charge, increases. Time constants typically range from a few milliseconds to tens of milliseconds. The time constant not only reflects the time needed to "charge" a membrane but also the time needed to discharge a membrane potential (Fig. 5-3). Thus one time constant after reaching its peak, a PSP will have decayed or fallen by 63% to 37% of its peak value.

Figure 5-2. The length constant is a measure of how far a potential travels along a cylinder before decaying to 37% of its original peak amplitude. A: One length constant from its origin, an EPSP of initial magnitude 1.00 has a peak magnitude of 0.37. B-D: By using a plumbing analogy, one can clearly see that either a leaky (low r_m , B) or narrow (high r_a , C) pipe results in a short length constant, whereas the opposite characteristics (high r_m and low r_a , D) result in a long length constant.

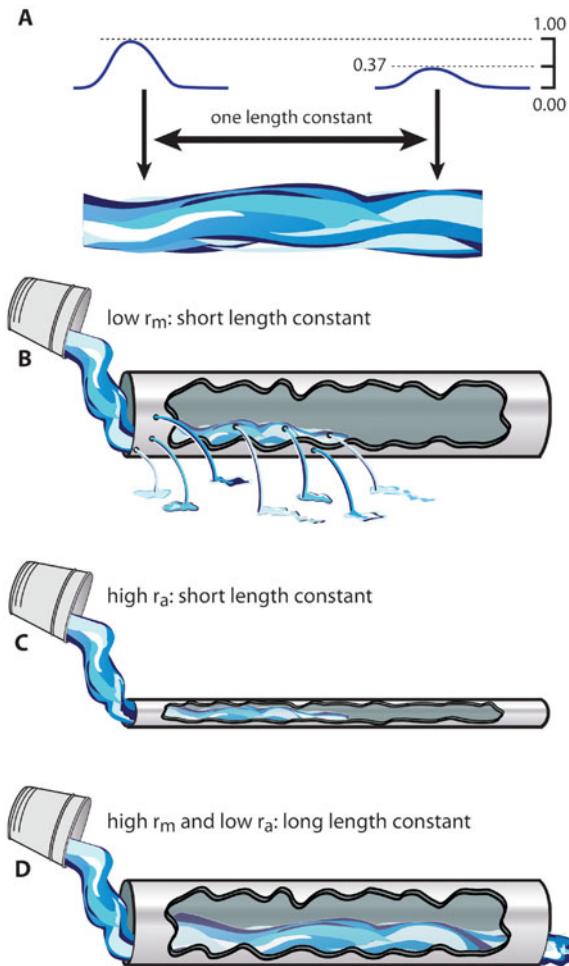
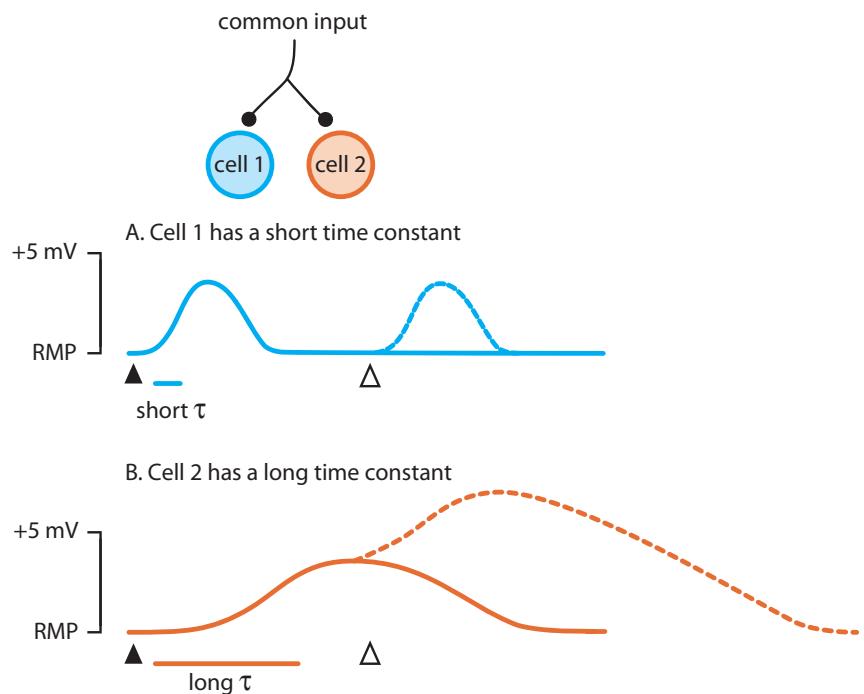


Figure 5-3. The time constant, τ , is the time needed for the membrane potential to reach 63% of its peak value. Consider two cells that differ only in their relative time constants. These cells receive the same synaptic input (inset at top). Cell 1 has a short time constant (solid line below trace), and its synaptic response reaches 63% of its maximal value after a shorter time (A) than does the synaptic response of cell 2 with a longer time constant (B). Furthermore, if a second input (hollow arrowhead) occurs shortly after the first input (filled arrowhead), then temporal summation (dashed lines in A-B) will only occur in cell 2, the cell with the long time constant. Cell 1, which has a short time constant, has the same response to both inputs. Thus, cells with longer time constants can summate inputs over a longer period of time.

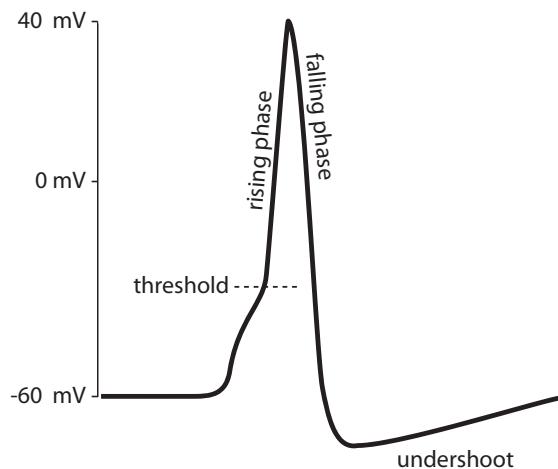


The formula for the time constant tells us that PSPs occur more rapidly in neurons with low membrane resistance. Also critical to the time constant or rapidity with which potential changes occur is the membrane capacitance. The higher the capacitance, or charge-storing capacity of a membrane, the longer is needed to charge the membrane. The membranes of neurons with low capacitance charge up rapidly and therefore, potential changes reach their peaks or troughs rapidly. In contrast, neurons with high-capacitance membranes charge up slowly, thereby stretching out the effect of a given synaptic input over a longer time. In reality, the membrane resistance of neurons is far more variable than the membrane capacitance. Regardless of what drives a difference in the time constant, inputs received over a longer period of time summate in neurons with a longer time constant, and only inputs received over a shorter period of time summate in neurons with a shorter time constant (Fig. 5-3).

IN MOST NEURONS, SPATIAL AND TEMPORAL SUMMATION THAT SUFFICIENTLY DEPOLARIZES A CELL RESULTS IN AN ACTION POTENTIAL

Incoming IPSPs and EPSPs sum, spatially and temporally, to alter a neuron's membrane potential. For a minority of neurons and sensory cells, the summation of PSPs alone determines the amount of transmitter released. In these cells, transmitter release is **graded**, with more transmitter released when the cell is depolarized and less when it is hyperpolarized. However, the vast majority of neurons employ an additional, very important mode of electrical signaling: the **action potential** (Fig. 5-4). In these cells, when the membrane reaches a certain depolarized **threshold**, an action potential, often termed a **spike**, results. Lord Edgar Adrian, who along with

Figure 5-4. During an action potential, the membrane potential shoots up from rest, anywhere from -70 mV to -50 mV , to a positive value before returning to rest. An undershoot or afterhyperpolarization occurs as the membrane potential initially repolarizes beyond the rest potential before eventually, and relatively slowly, returning to rest. The entire action potential occurs in one to a few milliseconds, with the rising phase occurring in under a millisecond.



Sir Charles Sherrington received the Nobel Prize for Physiology or Medicine in 1932, likened this process to the operation of a gun trigger. Pressure can build and build on the trigger but a bullet is fired only when pressure on the trigger passes a threshold. Just as a bullet's trajectory cannot be reversed once released, an action potential cannot be interrupted once it starts. We now turn to the action potential for the remainder of the chapter.

THE ACTION POTENTIAL IS AN ALL-OR-NONE UNIT OF EXCITATION

Most neurons send information across long enough distances, hundreds of length constants in many cases, that an electrical “boost” is needed to reach the synaptic terminal. The action potential provides the boost, allowing for transfer of information between the sometimes distant parts belonging to an individual neuron. The action potential also plays a key role in triggering communication from one neuron to another through chemical synapses. The action potential serves both of these functions because:

- It travels across long distances through action potential conduction

and

- The depolarization associated with the action potential triggers neurotransmitter release from synaptic terminals

Here, we consider the action potential and its conduction along neuronal processes. In the next chapter, we examine how the action potential affects neurotransmitter release machinery upon reaching the synaptic terminal.

As we learned in the last chapter, neurons receiving one or a few depolarizing inputs quickly return to the resting membrane potential. However, if the depolarizing input is sufficient to reach **threshold** (see much more below), then an enormous deviation from rest potential results. This deviation takes the cell's membrane potential from the rest potential to a positive potential and then back down to rest all within a few milliseconds (Fig. 5-4).

There are no half or partial action potentials. As an all-or-none signal, the action potential resembles the binary computer bit of information. A bit is either 0 or 1, never any fraction. As in computer language, information comes in the way that action potentials are strung together. The number and frequency of action potentials fired by a neuron within a **spike train**, meaning a sequence of spikes, code information just as strings of bits make up bytes and eventually kilobytes, megabytes, gigabytes, and terabytes of information. Understanding the exact nature of the neuronal code evidenced in a spike train remains an exciting challenge.

Box 5-2

SEVERAL NATURALLY OCCURRING AND DEADLY TOXINS TARGET THE VOLTAGE-GATED SODIUM CHANNELS (VGSCs).

Tetrodotoxin, often abbreviated as **TTX**, is a toxin produced by bacteria naturally present in a number of animals including pufferfish, newts, and sea stars. This powerful toxin derives its lethality from binding to the pore of VGSCs and thereby preventing the inward sodium current that generates action potentials. Tetrodotoxin has proved to be an invaluable tool in understanding VGSCs. Luckily, it presents only a minor medical threat; cases of tetrodotoxin poisoning in humans are rare and largely restricted to sushi eaters in Japan. In contrast, **saxitoxin** and **brevetoxin**, toxins that also target the VGSC pore, can present important health risks on occasion. Saxitoxin and brevetoxin are made by dinoflagellates, a type of plankton, and accumulate in shellfish. Sporadically, the population of plankton explodes, causing a **red tide** that ultimately leads to the illness and sometimes to the death of wildlife and humans that eat affected shellfish. The cause of death is respiratory failure due to paralysis for reasons that are described in Box 5-3.

A LARGE INCREASE IN SODIUM PERMEABILITY THROUGH VOLTAGE-GATED CHANNELS PRODUCES THE RISING PHASE OF THE ACTION POTENTIAL

The action potential can be understood using the same principles used to understand the rest potential. At the start of the action potential, sodium ion permeability increases to a level that is at least 20 times greater than the potassium ion permeability at rest. Because of this high sodium ion permeability, the membrane potential is then dominated by the Nernst potential for sodium ions, E_{Na} , which is +67 mV due to the far greater abundance of sodium ions outside of the cell relative to inside.

Sodium ion conductance during the rise of the action potential is carried by a special class of ion channels. Unlike the AMPA or GABA_A receptors, which are gated by the binding of a ligand such as a neurotransmitter, *voltage* gates the sodium channels responsible for the rapid rise of the action potential. Since depolarization itself activates **voltage-gated sodium channels (VGSCs)**, and since sodium ion influx depolarizes the cell, the sodium ion conductance is **regenerative**. In other words, sodium ion conductance through VGSCs feeds upon itself. Once past threshold, VGSC opening does not stop until virtually all VGSCs have opened. In fact, the threshold is the point at which VGSC opening becomes regenerative. Put another way, the opening of available VGSCs cannot be stopped once the action potential threshold is surpassed (see Box 5-2).

Because the permeability for sodium ions is so high, the action potential, at its maximum, overshoots zero and becomes positive. The peak of the action potential does not reach E_{Na} for a couple of reasons. First, during the rise of the action potential, so many VGSCs open that membrane resistance decreases, and at the same time, the driving force on sodium ions is reduced. As a result, sodium ion influx does not produce as large a voltage change as it would at rest potential. In addition, chloride and potassium channels that are open at rest remain open. At the positive potentials of the action potential, the driving force on chloride and potassium ions is greatly increased. Therefore, chloride ions enter the cell and potassium ions leave the cell, producing outward currents that antagonize the depolarization carried by VGSCs and keep the membrane potential from reaching E_{Na} .

VOLTAGE-GATED POTASSIUM CHANNELS REPOLARIZE THE MEMBRANE POTENTIAL AFTER THE PEAK OF AN ACTION POTENTIAL

Depolarization opens voltage-gated potassium channels as well as VGSCs. The channel carrying the ensuing potassium ion conductance, typically referred to as the **delayed rectifier**, opens after a delay and

does not contribute appreciably to the membrane potential until after the rising phase of the action potential is completed. Yet, soon after the action potential peak, voltage-gated potassium channels are maximally activated. The large potassium ion conductance carries potassium ions out of the cell, repolarizing the cell toward E_K . The potassium ion conductance develops slowly and lasts long enough to produce an **undershoot** or **afterhyperpolarization**, often abbreviated as **AHP**, which takes the membrane potential briefly toward E_K from rest (Fig. 5-4). Voltage-gated potassium channels are only triggered by depolarized potentials, so that once the membrane reaches potentials as hyperpolarized as the rest potential, the voltage-gated potassium ion conductance turns off. By repolarizing the membrane potential, the delayed rectifier contributes to terminating the action potential.

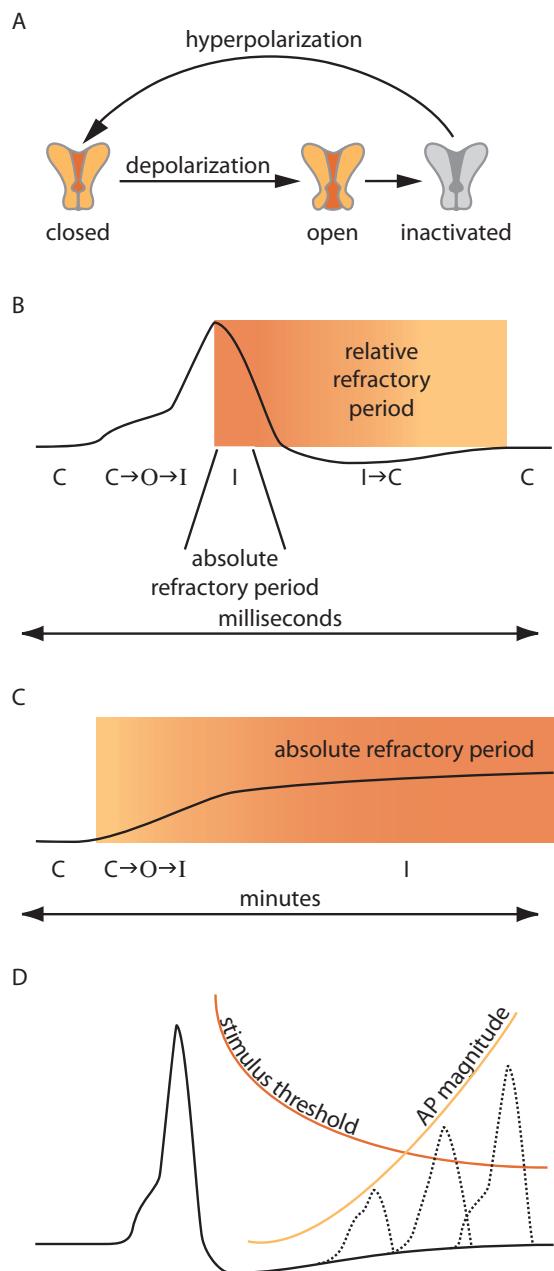
INACTIVATION OF VOLTAGE-GATED SODIUM CHANNELS ALSO CONTRIBUTES TO ACTION POTENTIAL TERMINATION

Beyond the delayed rectifier, there is another contributor to termination of the action potential: VGSC inactivation. Immediately after a brief opening, VGSCs **inactivate** (Fig. 5-5). Sodium ions cannot pass through the pore of an inactivated VGSC. More importantly, *an inactivated channel cannot open; it is not activatable*. To be activated again, a VGSC must return to a hyperpolarized voltage around the rest potential. Thus, even if there were no delayed rectifier conductance to repolarize the cell, the cell would slowly return to rest potential because the VGSCs would all inactivate and not reopen, while resting chloride and potassium ion conductances would repolarize the cell. The presence of voltage-gated potassium channels greatly accelerates the rate of membrane repolarization after an action potential.

THE THRESHOLD FOR AN ACTION POTENTIAL DEPENDS ON THE PROPORTION OF VGSCS THAT ARE INACTIVATED AND THEREFORE ON PRIOR ELECTRICAL HISTORY

De polarization above rest activates VGSCs. The larger the depolarization, the more VGSCs will open. *The action potential threshold represents the tipping point at which one more sodium ion entering the cell will trigger a regenerative sodium ion conductance and alternatively, one more potassium ion leaving the cell would take the cell back to rest potential.* The direction in which this unstable situation tips depends in large part on how many VGSCs are *closed* rather than inactivated. Remember that closed VGSCs, but not inactivated VGSCs, are available for opening (Fig. 5-5A). For example, if a large inward current takes the membrane

Figure 5-5. A: Voltage-gated sodium channels (VGSCs) change conformation from the closed (C) to the open (O) state when the membrane potential depolarizes above rest. Immediately after opening, VGSCs enter an inactivated (I) state. The transition from the open to the inactivated state is automatic and cannot be bypassed. To recover from inactivation and reenter the closed state, the membrane potential must hyperpolarize to near rest potential. B: The rapid opening of VGSCs ($C \rightarrow O$) is responsible for the rising phase of the action potential. Yet, VGSCs enter the inactivated state immediately after opening ($C \rightarrow O \rightarrow I$), rendering the membrane unexcitable because the inactivated VGSCs cannot open. During the decay phase of the action potential, most of the VGSCs are inactivated and there are not enough closed VGSCs to support an action potential; this period is the absolute refractory period. As the membrane potential approaches the rest potential, more and more VGSCs transition from inactivated to closed ($I \rightarrow C$), a period that is termed the relative refractory period. C: If a cell depolarizes slowly, over seconds to minutes, VGSCs open and become inactivated just as they do when a cell depolarizes quickly over a few milliseconds. However, in the case of a slow depolarization, no action potential can occur because not enough VGSCs are closed and available for opening once threshold is reached. Therefore, a slow depolarization leads to a persistent state of absolute refractoriness. D: When a cell repolarizes from an action potential to near the rest potential, the relative refractory period starts. During the relative refractory period, action potentials can occur. However, the depolarization needed to trigger an action potential (stimulus threshold) is greater than normal and the action potential peak (AP magnitude) is lower. After more and more time at a hyperpolarized potential, more and more VGSCs recover from inactivation, and consequently, the action potential returns to normal.



potential from rest to -40 mV in the course of a couple of milliseconds, an action potential is highly likely to occur (Fig. 5-5B). However, let us consider what would happen if a depolarization develops gradually over the course of minutes rather than milliseconds (Fig. 5-5C). As the membrane potential depolarizes ever so slightly, a few VGSCs open. After opening, these VGSCs inactivate. As long as the membrane potential does not hyperpolarize, more and more VGSCs open and then rapidly inactivate. If this process continues long enough, all of the VGSCs end up in the inactivated, or unopenable, state, at which point no amount of depolarization or inward current can trigger an action potential. Only after a hyperpolarization that allows the VGSCs to **recover from inactivation** and enter the closed state could an

Box 5-3

A FAILURE OF VOLTAGE-GATED SODIUM CHANNEL (VGSC) INACTIVATION CAN PRODUCE PARALYSIS.

The dependence of the action potential threshold on prior depolarizations has major implications for the hyperkalemic patient who we initially considered in Chapter 4. This patient's neurons would have a rest potential more depolarized than normal by a few millivolts, perhaps resulting in some errant neural functioning. However, far more worrisome are the consequences of elevated potassium ion levels for cardiac function. Contraction of cardiac muscle is driven by action potentials in cardiac muscle cells. Although the action potential of cardiac muscle differs substantially from that of a typical neuron, the rising phase is the same, carried by an influx of sodium ions through VGSCs. Thus, VGSCs are necessary for cardiac muscle action potentials that produce the cardiac muscle contractions necessary for life. How does an increase in extracellular potassium ion concentration from 5 to 7 mM affect cardiac function? Remember that cardiac muscle cells have a rest potential dominated by potassium ion conductance. Therefore, the rest potential of cardiac muscle cells would increase by almost 10 mV, greatly increasing the likelihood of VGSC opening and consequent inactivation. If enough VGSCs inactivate, action potentials and consequent muscle contractions cease. Therefore, if unrecognized and untreated, hyperkalemia is fatal.

A tissue-specific hyperkalemia occurs in patients with **hyperkalemic periodic paralysis**, an autosomal dominant disease. Patients with hyperkalemic periodic paralysis have a mutation in a VGSC allele that is expressed in skeletal muscle. Skeletal muscle cells fire action potentials, quite similar to neuronal ones, that drive individual muscle fiber contractions or **twitches**. The mutation in patients with hyperkalemic periodic paralysis blocks VGSC inactivation in skeletal muscle in the presence of an elevated potassium ion concentration. So, mutated channels that open *remain open* when in the presence of elevated potassium ions. Exercise results in elevated potassium ion levels around skeletal muscles. After exercise, the elevated potassium ion concentration depolarizes the muscle cells as described above. Mutant VGSCs open and stay open, keeping the membrane potential depolarized and preventing the normal VGSCs from recovering from inactivation after opening and subsequently inactivating. This renders the muscle unable to contract and consequently, patients with hyperkalemic periodic paralysis become weak, sometimes sufficiently so that they are unable to move (hence the name) immediately after exercise.

action potential once again occur. In this way, one can see that the action potential threshold depends not only on the voltage reached but also on the state of the VGSCs, which in turn depends on the cell's electrical history (see Box 5-3).

REFRACTORY PERIODS FOR ACTION POTENTIALS LIMIT THE RATE AT WHICH NEURONS CAN FIRE ACTION POTENTIALS

As should be clear by now, VGSCs in the inactivated state cannot open, even at depolarized potentials that would normally trigger an action potential. Therefore, immediately after a patch of membrane supports an action potential, that same area cannot support another action potential. The inability to fire

an action potential for 500 microseconds, a half a millisecond, or so after an initial action potential defines the **absolute refractory period** (Fig. 5-5). During the absolute refractory period, VGSCs are inactivated, unavailable to open, and therefore no amount of depolarizing current can trigger an action potential. The absolute refractory period ends when enough VGSCs leave the inactivated state upon repolarization of the membrane potential (Fig. 5-5). Thus VGSC inactivation is the root cause of the absolute refractory period.

After the membrane repolarizes from an action potential, more and more VGSCs transition from inactivation to a closed, but *activatable*, state. As VGSCs enter the closed state, they come back “online,” available once again to contribute to the rising phase of another action potential. At the same time as the VGSCs emerge from inactivation, conductance through voltage-gated potassium channels is very high, causing a hyperpolarization beyond the normal rest potential. During this afterhyperpolarization, a much larger inward current than normal is needed to reach the threshold for an action potential because of both the decrease in input resistance and the hyperpolarized membrane potential. This period, which lasts a few milliseconds, is termed the **relative refractory period** (Fig. 5-5D).

The length of the action potential, which varies across different neuronal types, determines the length of the refractory period. The lengths of the absolute and relative refractory periods in turn limit the rate at which neurons can fire action potentials. Since action potential durations vary from <1 ms to 3–4 ms, the maximum rate of firing varies from about 50 to one kHz, or 1,000 Hz, or more.

THE REFRACTORY PERIODS SERVE TO POLARIZE ACTION POTENTIAL CONDUCTION

Beyond providing an upper limit on the rate of neuronal firing, the absolute refractory period also provides directionality to action potential conduction. To understand this, consider the axon below that connects the soma and dendrites on the left to the synaptic terminal on the right:



An action potential initiated at point B may travel to both point A and point C because the axonal membrane between B and both A and C can support an action potential. However, once at A or C, the action potential cannot travel back to B since the membrane at B, as well as that between B and A or between B and C, is refractive. This example illustrates how *action potential conduction, rather than the axon itself, is polarized by the absolute refractory period*. Under physiological situations, an action potential starts in one place and travels in only one direction down neuronal processes, *away from where it has been*. In this way, the absolute refractory period is at the root of the electrical polarization of axons, originally introduced as Cajal’s law of dynamic polarization (see Chapter 2).

UNMYELINATED AXONS CONDUCT ACTION POTENTIALS AT SPEEDS PROPORTIONAL TO THEIR DIAMETER

An action potential travels along neuronal membranes because the inward sodium current at one spot depolarizes the adjacent membrane enough to start opening the VGSCs located there. Once the spike threshold is crossed, closed VGSCs open and a regenerative action potential occurs at the adjacent spot. In this fashion, *by sequentially activating VGSCs in adjacent membrane regions, action potentials travel down unmyelinated axons*. Consider the two-step process by which an action potential at site A results in an action potential at an adjacent site on the axon, B:

1. The inward current at A travels down the interior of the axon to reach B
2. The membrane at B depolarizes over time until it reaches the threshold for an action potential

The speed with which an action potential propagates down an axon, typically termed the **conduction velocity**, therefore depends inversely on the product of the axial resistance of the axon, r_a , and the capacitance of the axonal membrane, c_m :

$$\text{conduction velocity} \propto \frac{1}{r_a c_m}$$

Let us assume that the inside of an axon, **axoplasm**, is relatively uniform with respect to *resistance per given area*, a value termed **specific resistance**. Then, axial resistance will be greater in smaller-diameter fibers than in larger-diameter fibers or conversely, r_a will decrease as the cross-sectional area ($=\pi * \text{radius}^2$) of an axon increases. What this means is that action potentials will propagate faster in large-diameter axons, with low r_a values, than in small-diameter axons with high r_a values.

We also assume that neuronal membranes have relatively uniform capacitance per given membrane surface area, a value termed **specific capacitance**. Therefore, c_m will increase as the circumference ($=2 * \pi * \text{radius}$) of an axon increases, so that the capacitance of axonal membranes will be greater in larger-diameter fibers than in smaller-diameter fibers.

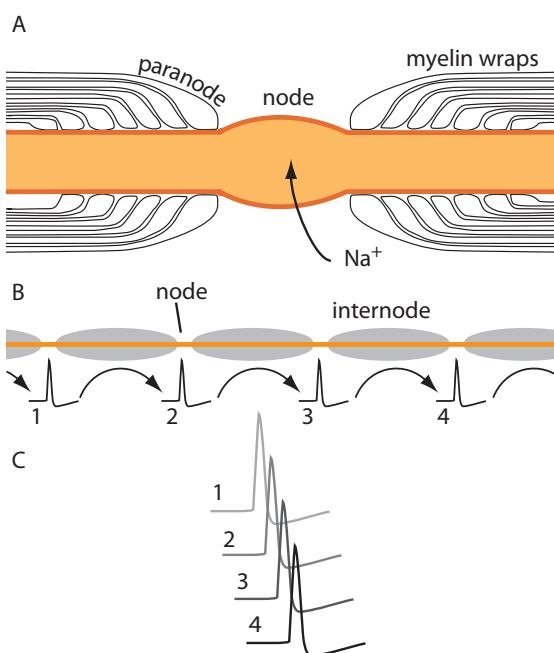
Since c_m increases in proportion to the radius and r_a decreases in proportion to the radius *squared*, conduction velocity, which is proportional to $1/r_a c_m$, will increase in proportion to the radius. Therefore, *action potential propagation is slower in smaller-diameter fibers and faster in larger-diameter fibers*. For both myelinated and unmyelinated axons, action potentials conduct more quickly down larger-diameter axons than smaller-diameter axons. In humans and other vertebrates, the range of unmyelinated axonal diameters and therefore of conduction velocities is limited. The largest unmyelinated axons are 1–2 microns in diameter and conduct at maximal speeds of 1–2 meters/second. Smaller unmyelinated axons, a half micron in diameter, conduct at speeds of about a half meter/second. Although conduction velocity is considerably faster in all myelinated axons for reasons detailed below, the same relationship exists, with larger myelinated fibers conducting action potentials more rapidly than do smaller myelinated fibers.

MYELINATION GREATLY INCREASES THE SPEED OF ACTION POTENTIAL CONDUCTION

As just mentioned, an action potential at one location in an unmyelinated axon will lead to the depolarization of adjacent regions of membrane. The depolarization travels most rapidly in large-diameter axons because r_a is lowest in these axons. In invertebrates, only axons that are *hundreds of microns in diameter* achieve the high conduction velocities needed for fast escape reactions. If vertebrates, including humans, were to use the same mechanism for ensuring rapid action potential conduction, we would have to be enormous—meaning large dinosaur size—to accommodate the large number of axons that we possess. Instead, vertebrates evolved a different mechanism, rather than size, to solve this problem. In vertebrates, *specialized glial cells make an insulating membrane termed myelin that wraps around axons and greatly speeds up conduction of action potentials.*

Axons wrapped by myelin are termed *myelinated axons*. Myelin is a membrane, containing mostly lipids, about 80% by weight, such as *galactocerebroside*, as well as proteins such as *myelin basic protein*. *Myelin, as well as the neuronal membrane that it covers, has few channels and thus has a high specific resistance, probably more than ten-fold higher than that of a typical neuronal membrane.* A myelin-producing cell wraps around a myelinated axon 10–160 times, more for larger axons and less for smaller-diameter axons. Each wrap of myelin consists of two lipid bilayers and the intervening cytoplasm (Fig. 5-6A). The lipid bilayers between two wraps are joined by extracellular *adherens junctions* (see Box 5-4), interspersed with the occasional *tight*

Figure 5-6. **A:** At axonal nodes, no myelin is present and VGSCs that are packed at high density support sodium ion influx during action potentials. In the paranode, the myelin wraps begin. The myelin wrapping around myelinated axons is restricted to the internodes. **B:** Action potentials move along a myelinated axon by saltatory conduction, meaning that the action potential jumps from one node to the next without depolarizing the internodes. In this example, the action potential is moving from left (1) to right (4). **C:** At any one moment, action potentials occur in multiple nodes (four are illustrated) as the rising phase of an action potential in one node leads to the depolarization of the next node, which then fires an action potential, which in turn depolarizes the subsequent node and so on. Action potentials are numbered for the node from which they arise, as labeled in B.



Box 5-4

SPECIALIZED JUNCTIONS KEEP MEMBRANES ADHERED TO ONE ANOTHER.

Adherens junctions are regions of cell-to-cell adhesion or more accurately membrane-to-membrane adhesion. A molecule spans each membrane and binds to a like molecule on the adjacent membrane within the extracellular space and to actin on the intracellular face. In the case of myelin, the membranes in the myelin wrap belong to the same glial cell. **Tight junctions** are occluding junctions that prevent fluid from flowing between two cell membranes. Importantly, tight junctions can allow small organic ions, such as potassium ions, to pass.

junction, both of which greatly increase the resistance of the myelin wrap while still allowing some small ions to pass through. Thus, the resistance of the axonal membrane is in series with an additional 20–320 high-resistance membranes beyond the axonal membrane. Since resistances in series add, the resistance between the inside of an axon and the outside of the myelin is huge, up to thousands of times greater than in a bare axon. The cytoplasm within the myelin-producing cell is squeezed out, so that the intracellular space is narrower than even the thickness of a single lipid bilayer, which in turn greatly increases *axial resistance* within the myelin sheath. The result of myelin's high membrane resistance, as well as the glial cell's high axial resistance, is that *no easy path exists along which current can escape*. Current cannot easily travel across the myelin wraps nor can it spiral down the center of the myelin-producing cell. This means that *the path of least resistance for an inward current due to an action potential is straight down the axon*.

Myelin does not cover the entire axon. Instead, myelin covers evenly spaced stretches, **internodes**, separated by patches of bare axon called **nodes of Ranvier** or simply **nodes** (Fig. 5-6). Voltage-gated sodium channels pack into the nodal membrane at densities of more than a thousand channels per square micron but are absent from the internodes. As a result of this channel distribution, nodes support action potentials and internodes do not. Because of the very high membrane resistance of the internodal region, action potentials *jump* from one node to the next, a process termed **saltatory conduction** (Fig. 5-6B–C).

In general, axons greater than about 1 or 2 microns in diameter are myelinated. The amount of myelin wrapped around an axon increases as the diameter of the axon increases, up to a maximal axon diameter of 20 microns or so in vertebrates including us. For example an axon with a diameter of 10 microns will be wrapped by about 7 microns of myelin. This axon will conduct action potentials at about 60 meters/second. The conduction velocities of myelinated fibers vary from about 5 to as much as 120 meters/second (see Box 5-5).

THE ACTION POTENTIAL BOOSTS NEURONAL COMMUNICATION

Numerous cell types beyond neurons employ the action potential. Most importantly, muscle cells fire action potentials that result in muscle contraction through **excitation-contraction coupling**. In certain glandular cells, action potentials trigger hormonal release. So, what makes the connection between neurons and their action potentials so special? The neuronal action potential serves long-distance communication well, an absolute requirement for a nervous system, for two reasons:

- Action potentials are self-perpetuating: An action potential in one stretch of membrane causes an action potential in the neighboring stretch of membrane.
- Action potentials travel in one direction.

DEMYELINATING DISEASES DISRUPT THE MYELIN WRAP AROUND AXONS.

Recall from Chapter 2 that peripheral myelin is produced by Schwann cells and central myelin by oligodendrocytes. There are differences not only in the way that oligodendrocytes and Schwann cells wrap axons but also in the molecular components of these two glial cell types. For this reason, **demyelinating diseases** affect either central or peripheral myelin, but not both. An example of a central demyelinating disease is **multiple sclerosis**, and examples of peripheral demyelinating disease include the acute inflammatory **Guillain Barré syndrome** and a heterogeneous group of progressive, hereditary neuropathies termed **Charcot-Marie-Tooth disease** or **hereditary sensory-motor neuropathy**. *The particular symptoms associated with demyelination depend on the identity of the axons affected.* Yet, mechanistic problems shared among demyelinating conditions include:

- Slow conduction speed that perturbs the information conveyed by carefully timed action potentials

- Failure of some action potentials to propagate
- Metabolic costs associated with restructuring the axon

Along with the diversity of symptoms caused by demyelinating diseases, the pathophysiology varies across and even within a disease such as Charcot-Marie-Tooth disease. For example, some forms of the disease result from a defect in the axon, and other forms from a defect in the myelinating glial cell. Regardless of whether the initial defect affects the axonal membrane or the myelinating glial cell, the end result is a loss of myelination and the consequent disruption to neuronal communication.

Thus, by virtue of the action potential, neurons with processes of up to 2 meters achieve the remarkable ability to reliably and rapidly send information gathered at one end all the way to the other end.



ADDITIONAL READINGS

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CHAPTER 6

NEUROTRANSMITTER RELEASE

Once a neuron sums up and integrates all incoming information into a coherent message, the neuron *sends* that message on to another cell or cells via synapses. In this chapter, we examine the biochemical events that allow neurons to send a chemical message to a postsynaptic cell.

Key to neurotransmitter release is the packaging of neurotransmitters into **synaptic vesicles**. With a few exceptions, discussed in the next chapter, neurotransmitters are released from synaptic vesicles rather than from the cytosol. Synaptic vesicles are spherical organelles (30–100 nm in diameter), packed with thousands of neurotransmitter molecules. Before diving into the details of neurotransmitter release, we consider an overview of the release process (Fig. 6-1) that we then examine step by step:

- Depolarization of the synaptic terminal triggers calcium ion influx through **voltage-gated calcium channels**.
- Voltage-gated calcium channels sit in near proximity to specialized regions of the plasma membrane called **active zones**.
- A small number of synaptic vesicles **docked** at each active zone are “primed,” meaning that they are ready to be released.
- Several proteins make up a **SNAREpin** that tethers docked synaptic vesicles to the plasma membrane.
- Calcium ion influx triggers a conformational change in the SNAREpin, which results in **fusion** of the synaptic vesicle to the plasma membrane. This results in the formation of a **fusion pore**.
- The fusion pore allows neurotransmitter contained within the vesicles to diffuse into the synaptic cleft (see Fig. 2-3C), the extracellular gap between pre- and postsynaptic cells.
- The membrane of the emptied synaptic vesicle, now continuous with the plasma membrane, is **endocytosed** to be **recycled** and refilled as the SNAREpin disengages and docks a new synaptic vesicle.

Although we are most interested in neurotransmitter release per se, the actual release of neurotransmitter is relatively trivial—transmitter simply diffuses from

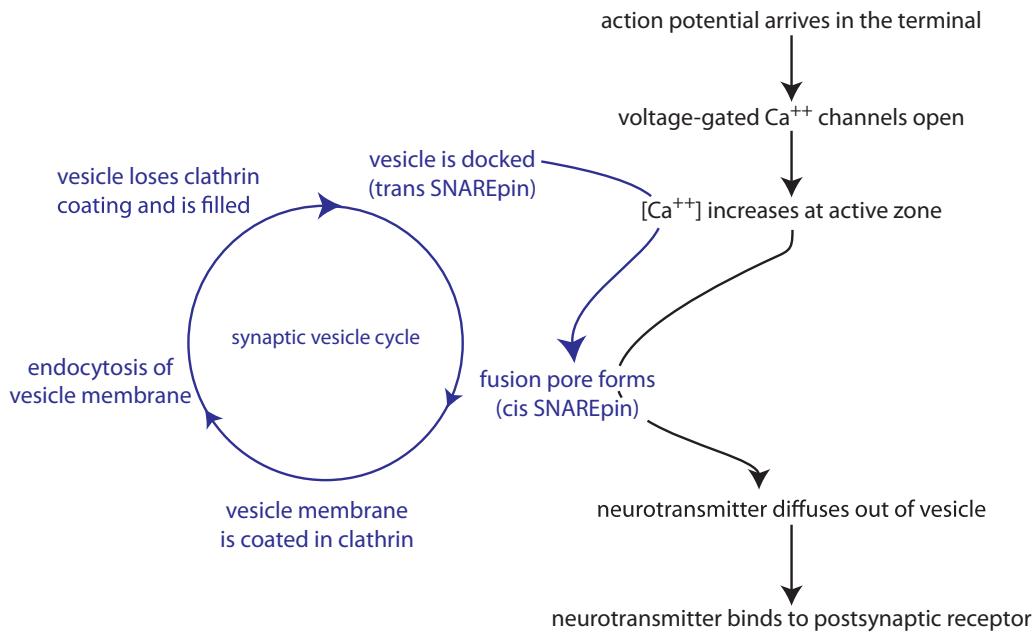


Figure 6-1. Neurotransmitter release involves the coordination of neuronal activity (black on right) with synaptic vesicle cycling (blue on left) and ultimately the formation of a fusion pore. Synaptic vesicles cycle through formation, fusion, and endocytosis for reuse. When an action potential arrives in the synaptic terminal, calcium ion influx is triggered, and a high concentration of calcium ions is reached locally. The high concentration of calcium ions at the site of docked synaptic vesicles triggers a conformational change in the SNAREpin that holds a docked vesicle close to the plasma membrane. When the SNAREpin adopts the cis configuration, a fusion pore forms and neurotransmitter, contained within the synaptic vesicles, diffuses out. Neurotransmitter ultimately reaches receptors in the postsynaptic membrane (see Chapter 8) to complete the communication from presynaptic to postsynaptic cell.

a vesicle into the synaptic cleft through an opening or pore—compared to the complex process of *membrane fusion* that allows for formation of a pore and subsequent neurotransmitter release. Consequently, this chapter focuses on the process of triggered membrane fusion.

There are two fundamentally different types of synaptic vesicles and consequently two processes of neurotransmitter release. In this chapter, we focus on the more common process, the release of small, low-molecular-weight neurotransmitters (see Chapter 7) such as glutamate or γ -aminobutyric acid (GABA), from small, clear synaptic vesicles. There are relatively few species, or types, of low-molecular-weight transmitters. Yet, these transmitters are ubiquitous, present in all, or nearly all, synaptic terminals in the nervous system. The release of low-molecular-weight neurotransmitters from small synaptic vesicles is tightly regulated, so that release accompanies neuronal activity whereas release from inactive neurons is rare. In the final section of this chapter, we consider the release of a different class of neurotransmitter, the neuropeptides, from large, dense-core vesicles. The type of neuronal activity that triggers release from large vesicles, as well as the molecular details of this release, differs substantially from the process of release from small synaptic vesicles.

MEMBRANE FUSION IS A PROCESS PRACTICED BY ALL CELLS

Membrane fusion is a complex and fundamental process that occurs **constitutively**, meaning all the time, in all cells. Constitutive membrane fusion serves basic cell biological functions such as the synthesis and trafficking of proteins through the endoplasmic reticulum and Golgi apparatus, the construction of internal organelles, and cell division. Unlike constitutive membrane fusion, *membrane fusion associated with the release of neurotransmitters must be tightly controlled, so that it occurs when triggered, usually by an action potential.* To provide control over membrane fusion, two different proteins regulate the fusion of synaptic and plasma membranes:

- **Complexin** suppresses constitutive fusion.
- **Synaptotagmin** senses the calcium ion concentration within the *immediate* vicinity of the active zone, and when this concentration reaches a threshold level, it releases fusion from constitutive suppression.

As membrane fusion events occur constitutively throughout all cells, as well as during calcium ion-triggered neurotransmitter release from neurons, membrane fusion is clearly essential for life. Perhaps because of the critical roles played by membrane fusion and perhaps because the machinery is located intracellularly, there are few, if any, inherited or autoimmune diseases that involve a primary defect in membrane fusion machinery. Instead, numerous bacteria and predatory animals have evolved the ability to synthesize, accumulate, and use toxins and venoms that disable membrane fusion to either stun or kill their hosts and prey (see more below).

THE DRIVING FORCE FOR CALCIUM IONS ALWAYS MOVES CALCIUM IONS INTO THE CELL

Calcium ions are more concentrated, by at least a thousand-fold, outside of neurons than in the cytosol. Unlike other ions, most of the calcium ions within a neuron are sequestered in intracellular **stores** or deposits rather than existing as free ions in the cytosol. The endoplasmic reticulum and mitochondria store calcium ions at a far higher concentration than the 10–100 nM concentration found in cytosol. Since extracellular calcium ion concentration is roughly 2–5 mM, the calculated Nernst potential for calcium ions is a potential of hundreds of millivolts, much more depolarized than even the peak of the action potential. This Nernst potential indicates that when calcium-permeable channels open, calcium ions will always enter the cell and will do so with a great deal of driving force.

Box 6-1

THE WAVEFORM OF THE ALL-OR-NONE ACTION POTENTIAL CAN VARY, WHICH MEANS THAT THE CALCIUM ION INFUX VARIES.

In Chapter 5, the action potential was introduced as an all-or-none phenomenon. Although this is true, the effect of an action potential varies both across cells and across conditions within individual cells. Depending on its particular waveform or time course, an action potential causes more or less calcium ion entry into the synaptic terminal (Fig. 6-1). The longer an action potential lasts, the more calcium ion influx occurs. The amount of calcium ion influx in turn determines the amount of transmitter released, so that as more calcium ions enter the cell, more neurotransmitter is released. Thus, the end result of the action potential, the amount of neurotransmitter released, can vary between action potentials with different time courses.

DEPOLARIZATION ACTIVATES VOLTAGE-GATED CALCIUM CHANNELS TO TRIGGER NEUROTRANSMITTER RELEASE

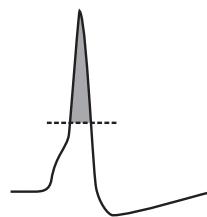
A depolarization from rest to about -20 mV activates calcium channels that, like sodium channels, are gated by a depolarized voltage. However, unlike sodium channels, *calcium channels do not rapidly inactivate but rather remain open for as long as the membrane is sufficiently depolarized*. Consequently, long-lasting action potentials result in more calcium ion influx than briefer action potentials (Fig. 6-2); more calcium ion influx in turn results in more transmitter release (see Box 6-1). Note that the depolarization needed to open calcium channels can arise from an action potential invading the synaptic terminal, as is the case for most neurons, or from a graded depolarization in the case of non-spiking neurons.

Calcium ions entering a synaptic terminal act very locally. Active zones (Fig. 6-3), the sites at which neurotransmitter is released, are marked by the presence of:

- Voltage-gated calcium channels
- A specialized stretch of plasma membrane
- Cytoskeletal components that keep synaptic vesicles tethered close to the plasma membrane

Across the synaptic cleft from each active zone, concentrations of receptors crowd the postsynaptic cell membrane (Fig. 6-3). At the active zone, calcium channels are located adjacent to sites where small synaptic vesicles are docked and where membrane fusion occurs. Because of this architecture, a high concentration

A. Brief action potential permits little Ca^{++} influx



B. Prolonged action potential enables greater Ca^{++} influx

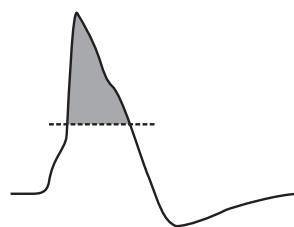


Figure 6-2. Short-duration action potentials (A) spend less time above the voltage threshold (dashed line) for voltage-gated calcium channels (gray) than do longer-duration action potentials (B). As a result, fewer calcium channels open, fewer calcium ions enter the cell, and less neurotransmitter release results.

of calcium ions within the active zone triggers fusion of the plasma and synaptic membranes (Fig. 6-4C) even when calcium ion concentration within the total cytosol of the neuron remains unchanged. Thus *neurotransmitter release is triggered by a very high and very localized concentration of calcium ions*. (see Box 6-2.)

The **synaptic delay**, the time between a presynaptic action potential and a postsynaptic response, is less than a millisecond. The vast majority of the synaptic delay involves the time needed for an incoming signal to trigger calcium ion influx and then membrane fusion. Diffusion of neurotransmitter across the synaptic cleft and activation of postsynaptic receptors require far less time.

SYNAPTIC VESICLES ARE HELD CLOSE TO THE PLASMA MEMBRANE AT ACTIVE ZONES BY COMPLEXES OF SNARE PROTEINS

Three SNARE proteins make up a SNAREpin. There are two classes of SNARE proteins:

- **v-SNAREs** are present in the synaptic vesicle membrane.
- **t-SNAREs** are present in the target or plasma membrane.

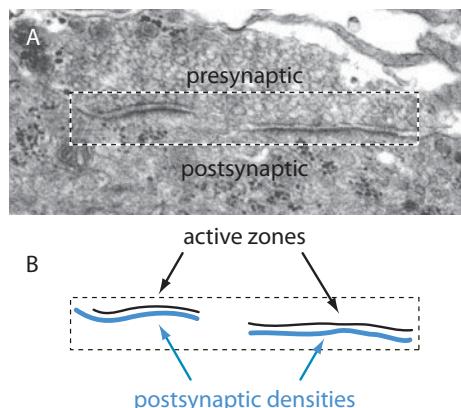
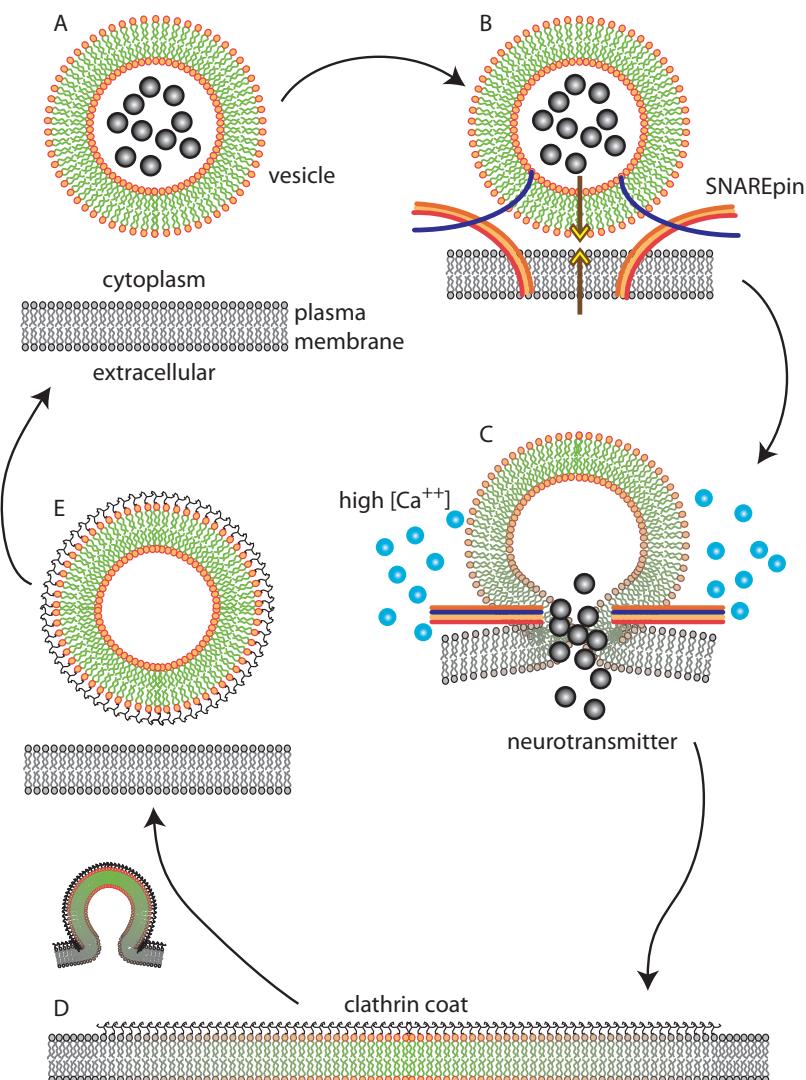


Figure 6-3. In this electron micrograph (A), a large number of clear synaptic vesicles are bunched in one terminal around two active zones (see locations in B). Both the active zone and the postsynaptic density are electron-dense and therefore show up dark in the electron microscope. The presynaptic density marking the active zone is crowded with calcium channels and the postsynaptic density is crowded with receptors (see Chapter 8). Motoneuron terminals at the neuromuscular junction have hundreds of active zones, whereas central terminals typically have one. The synapse shown here is from a sympathetic ganglion, where a few active zones typically mark each terminal.

Modified from Lysakowski, A., H. Figueras, S.D. Price, and Y.-Y. Peng. *J Comp Neurol* 403: 378–390, 1999, with permission of the publisher, John Wiley & Sons.

Figure 6-4. Clear synaptic vesicles fuse to the plasma membrane, releasing their contents into the extracellular space, and then are recycled by budding off of the plasma membrane. When a synaptic vesicle (A) moves close to the plasma membrane, it is docked to the plasma membrane by a SNAREpin (B). In the *trans* configuration (SNAREpins in B), the helices of the SNAREpin are partially zipped up, and they exert forces (brown and yellow arrows) that hold the synaptic vesicle close to the plasma membrane. C: When a high concentration of calcium ions (blue circles) is reached in the immediate vicinity of the docked vesicle, the SNAREpin zips up completely into a *cis*-SNARE (SNAREpins in C), causing the vesicle and plasma membranes to fuse and a pore to form. The formation of a pore allows neurotransmitter (black dots) to diffuse out of the vesicle. D: The vesicle membrane is covered in a clathrin coat and flattens out, becoming continuous with the plasma membrane before endocytosing. E: The clathrin coat around the outside of the endocytosed (inset along arrow from D to E) membrane facilitates the formation of a spherical vesicle. The recycled vesicle (E) originally has a clathrin coat. The clathrin coat is lost and the vesicle filled with neurotransmitter (A) before docking again (B) to start another cycle of release.



Neurotransmitter release depends on two t-SNAREs and one v-SNARE:

- The t-SNAREs are **SNAP-25** and **syntaxin**.
- The v-SNARE involved in neurotransmitter release is **synaptobrevin**, which is alternatively called **vesicle-associated membrane protein** or **VAMP**.

SNAP-25 and syntaxin, anchored within the plasma membrane form a bundle, or SNAREpin, with synaptobrevin anchored within the synaptic vesicle membrane. In the **trans-SNARE** configuration, the SNAREpin holds the vesicle membrane close to but distinct from the plasma membrane (Fig. 6-4B). Once the calcium ion trigger for fusion arrives, the SNARE bundle “zips up” into the **cis-SNARE** configuration, resulting in fusion of the two lipid bilayers and consequently a pore that opens from the inside of the synaptic vesicle to the extracellular space of the synaptic cleft (Fig. 6-4C). The neurotransmitter contained within the vesicle then simply diffuses out into the synaptic cleft (see Box 6-3 and Box 6-4).

Box 6-2

A LOSS OF CALCIUM CHANNELS IN TERMINALS WILL IMPAIR ACTION POTENTIAL-TRIGGERED SYNAPTIC RELEASE OF NEUROTRANSMITTER.

Patients with **Lambert-Eaton syndrome**, a rare autoimmune disease, make antibodies directed against a subset of voltage-gated calcium channels critical to triggering synaptic release of neurotransmitter. This deficit greatly impairs the calcium-triggered release of neurotransmitter. However, spontaneous release of neurotransmitter due to constitutive activity in the release machinery continues normally. Since the antibodies involved in Lambert-Eaton syndrome do not cross the blood–brain barrier, only peripheral terminals are affected. Most affected are the somatomotor and autonomic terminals releasing **acetylcholine**, although sympathetic terminals releasing norepinephrine are also affected but less so. Patients typically present with motor weakness as their chief complaint. This is because as the number

of functional voltage-gated calcium channels in the motoneuron terminal decreases, each action potential results in less neurotransmitter release and therefore less muscle contraction. Diagnostic of Lambert-Eaton syndrome is an increasing or **incremental response** to repeated stimulation in diagnostic testing. The increasing response occurs because calcium ions, entering through the remaining voltage-gated calcium channels, progressively build up in the motoneuron terminal, eventually reaching required levels. Thus, repeated stimulation circumvents the primary defect. Treating patients with **diaminopyridine**, a potassium channel blocker, is an effective therapeutic, as it increases calcium ion influx by blocking repolarization and thereby prolonging the action potential.

The energy needed to fuse vesicle and plasma membranes is provided by the energy-releasing conformational change of zipping up the multiple SNAREpins that dock each synaptic vesicle to the active zone. Returning the molecular components of the SNAREpins to their unzipped forms requires energy that is provided by a specific ATPase, termed **NSF**. Tethering synaptic vesicles in place allows for rapid membrane fusion and thus quick neurotransmitter release upon receiving a sufficient calcium ion signal (Fig. 6-4).

CALCIUM ION INFUX INITIATES THE SYNCHRONOUS RELEASE OF VESICLES

Recall that to link membrane fusion to depolarization, *complexin suppresses constitutive fusion and synaptotagmin releases fusion from constitutive suppression when the calcium ion concentration reaches a sufficient local concentration*. Although complexin serves to suppress constitutive neurotransmitter release from presynaptic terminals, a small amount of constitutive release occurs, so that single synaptic vesicles are infrequently released from terminals. Like calcium-triggered release, constitutive release depends on membrane fusion but is not dependent on calcium ion influx into the presynaptic terminal. Control is accomplished by

CLOSTRIDIAL TOXINS STOP SYNAPTIC TRANSMISSION BY CLEAVING ONE OF THE SNAREPIN PROTEINS.

Botulinum toxin, produced by the anaerobic bacterium *Clostridium botulinum*, originally found in rotten meat, binds to neuronal membranes and is endocytosed. The toxin appears to be preferentially endocytosed by neurons utilizing acetylcholine as their transmitter, a group that includes somatic motoneurons, autonomic motor neurons, postganglionic parasympathetic neurons, and sympathetic ganglion cells that innervate sweat glands (see Chapter 7). Once inside the cell, botulinum toxin cleaves one of the molecules in the SNAREpin. Three strains of the toxin, including the one most widely used for therapeutic purposes, cleave SNAP-25, four strains cleave synaptobrevin and one cleaves syntaxin. Cleavage of any part of the SNARE complex prevents neurons from releasing neurotransmitter. Since it is preferentially taken up by motoneurons that utilize acetylcholine as their transmitter, botulinum toxin kills people by preventing the acetylcholine release necessary for breathing. There is no treatment save for placing patients on a ventilator and waiting the weeks or months, dependent on the strain involved, that it takes to break down and clear the toxin.

Despite its powerful lethality, botulinum toxin is used at very low doses as a treatment for a variety of medical conditions including **strabismus** or crossed eyes, **blepharospasm** or excessive blinking, **laryngeal dystonia** or spasm of the vocal cords, and even certain types of **incontinence**. Even more widespread than modified botulinum's therapeutic uses are its cosmetic uses, chiefly for the erasure of wrinkles. This latter use works because wrinkles are sustained by motoneuron-produced muscle contractions! Therefore, injection of modified botulinum into and near wrinkles blocks release of acetylcholine from motoneurons and therefore blocks activation of the facial muscles involved. The pharmaceutical relaxation of wrinkles lasts for months, as long as it takes to clear the injected toxin, typically strain A. The "safety" of injecting one of the most threatening agents of biological warfare into healthy people requires the usage of extremely low doses in restricted locales. Even so, reports of patients leaving a physician's office after receiving an injection of botulinum toxin for forehead wrinkles with an entirely frozen face are not uncommon.

complexin's stabilization of the trans-SNARE configuration, holding synaptic vesicles in a state of readiness for immediate release. Essentially, complexin *freezes* the SNAREpin in the trans configuration, greatly disfavoring constitutive release.

Working in concert with complexin is synaptotagmin, a calcium ion-sensing molecule, that senses the rise in calcium ion concentration at active zones. When this rise is sufficient, synaptotagmin interacts with the SNAREpin to trigger the coordinated and synchronous fusion of synaptic vesicles with the presynaptic membrane. *By facilitating the trans- to cis-SNARE transition, synaptotagmin favors fusion and neurotransmitter release.* Thus, when the presynaptic terminal depolarizes and calcium ions enter the terminal, neurotransmitter release occurs rapidly and reliably.

Together, complexin and synaptotagmin regulate the fusion of vesicular and plasma membranes and thus couple neurotransmitter release to depolarization. At rest, complexin's actions dominate, and a small amount of neurotransmitter is released intermittently and in a calcium ion-independent manner. However, when

TETANUS TOXIN IS TRANSPORTED INTO A PARTICULAR CELL TYPE IN THE SPINAL CORD WHERE IT CLEAVES A SNAREPIN PROTEIN.

Another clostridial species, *Clostridium tetani*, produces **tetanus toxin**. Like botulinum toxin, tetanus toxin enters neurons and cleaves a molecule in the SNARE complex, in this case synaptobrevin. Unlike botulinum toxin, tetanus toxin is transported retrogradely, meaning against the normal direction of action potential conduction, *from* the terminal *to* the soma. Tetanus toxin is taken up by motoneuron terminals, taken back to the motoneuron soma, and then further transported, again retrogradely, *across* the synaptic cleft to presynaptic terminals belonging to inhibitory interneurons. The inhibitory interneuron is the site where tetanus toxin exerts its pathogenic effects. The mechanisms targeting tetanus toxin specifically to the presynaptic

terminals of inhibitory interneurons are not known. Nonetheless, once in the inhibitory interneuron terminals, tetanus toxin prevents neurotransmitter release, thereby releasing postsynaptic motoneurons from all inhibitory control. The result is continuous motoneuron discharge and consequently unremitting muscle contractions causing **lockjaw** and **opisthotonus**, a characteristic arching of the back, memorialized in a powerfully emotive painting by the Scottish painter, Charles Bell (Fig. 6-5). *Muscle contractions due to tetanus are sufficiently severe that they cause severe pain and can even break bones.* Luckily, tetanus vaccine is effective and widespread, rendering tetanus a disease largely of the past.

Figure 6-5. This painting, *Opisthotonus*, by Charles Bell, shows an individual suffering from tetanus. Extensor muscles (see Section 5) are most affected, resulting in hyperextension. Opisthotonus is the term applied to a posture balanced on the heels of the feet and the crown of the head. This posture is a classic sign of severe tetanus.

Photograph kindly provided by the Royal College of Scottish Surgeons of Edinburgh.



an action potential triggers sufficient calcium ion influx, synaptotagmin breaks complexin's hold on the SNAREpin. Synaptotagmin favors the zipping up of SNARE proteins into the *cis* configuration. As a result, a fusion pore is formed and neurotransmitter spills into the synaptic cleft. Importantly, synaptotagmin-mediated neurotransmitter release, which is entirely calcium-dependent, occurs with high probability at depolarized active zones.

Box 6-5

KISS-AND-RUN TRANSMISSION ALLOWS FOR THE RELEASE OF ONLY A FRACTION OF A VESICLE'S NEUROTRANSMITTER CONTENT.

There is one exception to the vesicle as unit-of-release rule: so-called **kiss-and-run** release. In kiss-and-run, a fusion pore forms but then quickly closes so that the amount of neurotransmitter released is a fraction of a vesicle's content. As a result of kiss-and-run release, the smallest molecules contained in the vesicle, typically the neurotransmitter, diffuse into the synaptic cleft preferentially. Larger molecules, also present in many synaptic vesicles (see Chapter 7) and more costly to synthesize in terms of both energy and time, may not leak out during kiss-and-run release. It remains unclear, indeed controversial, how often kiss-and-run release occurs at neuronal synapses and what advantages, if any, it may confer.

Box 6-6

VESICLES COME IN TWO VARIETIES.

As mentioned at the beginning of the chapter, small vesicles contain low-molecular-weight neurotransmitters and large vesicles contain small peptide neurotransmitters. Although large vesicles are the only packaging for peptide neurotransmitters, they often also contain adenosine triphosphate (ATP) and low-molecular-weight neurotransmitters as well.

NEUROTRANSMITTER IS RELEASED IN QUANTAL PACKETS CONTAINED WITHIN VESICLES

The vesicle is the unit of information used by the chemical synapse (see Box 6-5). Upon sufficient depolarization, some number of small vesicles (see Box 6-6) fuse with the plasma membrane and dump their chemical contents into the **synaptic cleft**. The average number of vesicles released per action potential varies from hundreds at the **neuromuscular junction** to one at many, if not most, central synapses. A difference in the number of active zones per synapse largely explains this variation. Many central synapses, such as those in the hippocampus, contain a single active zone, whereas the neuromuscular junction contains hundreds of active zones.

When a single action potential arrives at an active zone, either a vesicle is released or no vesicle is released. Put into probabilistic terms, the probability of release can vary between zero—release at an active zone never happens—and one—release happens in response to every action potential. Release probability at hippocampal synapses is roughly 0.5, whereas at other, more reliable synapses, such as the neuromuscular junction, release probability may approach 0.8 or so.

The lower number of active zones and thus vesicles released at central synapses enables one postsynaptic cell to receive and sum up information from multiple inputs. A low number of active zones per synapse and thus a low number of vesicles released per action potential prevents a **ceiling effect** for each synaptic input, meaning that the cell is not maximally affected by input at any one synapse. Because one input cannot saturate, or even come close to saturating, the postsynaptic response, inputs from an increasing number of excitatory inputs produce an increasingly large response. In practice, most central neurons integrate thousands of inputs without reaching a maximal or saturated response level. This wide **dynamic range**, the range of inputs over which a response varies, is critical in sensation, allowing us to, for example, hear a whisper as a quiet sound and a jet's takeoff as a loud sound. A wide dynamic range also enables us to contract a muscle to produce a force that varies between very low—enough to stroke a baby's cheek—to very high—enough to open a tightly sealed jar. Beyond these examples, all neurons operate within a dynamic range that is sufficient to allow for graded responses to graded inputs.

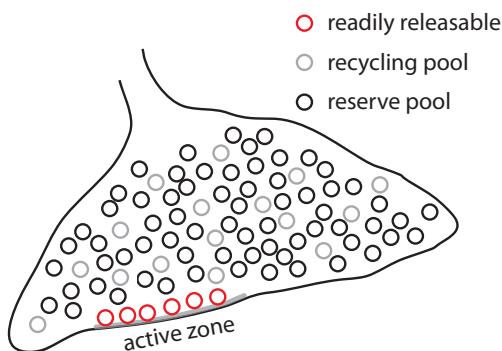
Integration of numerous inputs is not needed at the neuromuscular junction where only one motoneuron axon makes a single contact with each postsynaptic muscle fiber (see Chapter 21). Yet, a motoneuron endplate contains many active zones. Since one vesicle is released at each active zone, and there are hundreds of active zones, hundreds of vesicles are released per action potential in the presynaptic axon. This arrangement prevents a **floor effect**, meaning that when an action potential arrives in the motoneuron, the sole input to a muscle fiber, the input will not be so small that no effect occurs in the muscle. Thus, an action potential in the motoneuron innervating a skeletal muscle reliably causes a muscle fiber twitch.

THE POOL OF READILY RELEASABLE SYNAPTIC VESICLES IS REPLENISHED AFTER SYNAPTIC ACTIVITY

As should be clear by now, once sufficient calcium ion influx occurs, docked synaptic vesicles fuse and release neurotransmitter into the synaptic cleft. Because the synaptic vesicles abutting the membrane at the active zone are the ones released upon depolarization and calcium ion entry, these synaptic vesicles form the terminal's **readily releasable pool** (Fig. 6-6). The proportion of vesicles that is readily releasable is low, generally less than 2% of the synaptic vesicle population. Because of its small size, the readily releasable pool could, in theory, be depleted by fewer than two dozen action potentials occurring at **high frequency**, meaning in rapid succession. However, as one may imagine, depletion does not occur as there is a mechanism to **replenish** the readily releasable pool, by recycling released vesicles (Figs. 6-1 and 6-4). After a synaptic vesicle at the active zone fuses to the plasma membrane and empties its contents, it merges with the plasma membrane en route to having its membrane recycled. The stretch of membrane, containing mostly membrane from the fused vesicle, is endocytosed in a process that takes seconds and is then recycled to make a synaptic vesicle (Fig. 6-4). The amount of membrane that buds off is about the same as the amount of membrane contained within a synaptic vesicle. **Clathrin**, a protein that self-assembles into basket-like structures, coats the inside of the plasma membrane at the active zone and facilitates the formation of vesicles from membrane endocytosed at the active zone. Recycled vesicles are then refilled with neurotransmitter through processes described in Chapter 7. Recycled vesicles comprise a **recycling pool**, consisting of 10%–20% of the total number of synaptic vesicles in the synaptic terminal. Note that the recycling pool denotes a functional distinction, vesicles that were recently released and then rapidly endocytosed and recycled, but not a spatial one as the recycling vesicles are found interspersed with vesicles of a final group of synaptic vesicles, the **reserve pool** (see more below and Fig. 6-6).

The recycling pool of vesicles not only arises from vesicles recycled from the readily releasable pool but also feeds the readily releasable pool. Thus, the readily releasable pool receives a constant influx of vesicles from the **recycling pool**, thereby ensuring the availability of enough vesicles for fusion upon a subsequent depolarization and preventing depletion of releasable synaptic vesicles from the synaptic terminal.

Figure 6-6. Synaptic vesicles that are docked and primed for release form the readily releasable pool. After fusing to the plasma membrane, the membrane from synaptic vesicles of the readily releasable pool is endocytosed. The endocytosed vesicles form the recycling pool, which is scattered throughout the synaptic terminal and which ultimately replaces the depleted readily releasable pool. The majority of synaptic vesicles in the synaptic terminal belong to the reserve pool. Reserve vesicles are tethered to the internal cytoskeleton and only move to the active zone under extremely active conditions.



To summarize, under normal circumstances, an action potential arriving in the synaptic terminal sets in motion the recycling cycle:

- An action potential arrives and a readily releasable vesicle fuses to the plasma membrane.
- The membrane of the released vesicle, coated with clathrin, is endocytosed and joins the recycling pool.
- A vesicle from the recycling pool moves toward the active zone and is docked, thereby joining the readily releasable pool of vesicles.

In this way, vesicle movement from the recycling pool to the readily releasable pool replenishes the pool of readily releasable synaptic vesicles docked at the active zone when needed.

A LARGE RESERVE POOL OF SYNAPTIC VESICLES SUPPLIES VESICLES WHEN HIGH-FREQUENCY RELEASE DEPLETES THE RECYCLING POOL

The vast majority of synaptic vesicles, 80%–90% of the total, belong to the reserve pool. The reserve pool is not tethered closely to the active zone but is intermingled with vesicles of the recycling pool. Under circumstances of unusually high activity, the recycling pool becomes depleted, and vesicles from the reserve pool are recruited to the active zone for release. At rest, molecules called **synapsins** tether reserve pool synaptic vesicles to the cytoskeleton. Upon strong stimulation, a high concentration of calcium ions reaches the synaptic terminal's free cytosol, not only the region just inside the active zone membrane. High calcium ion concentration in the terminal triggers the phosphorylation of synapsin. When phosphorylated, synapsin releases the reserve pool's synaptic vesicles from their tether to the cytoskeleton so they can then move to the active zone and be primed for release.

After fusion with the plasma membrane, synaptic vesicles of the reserve pool recycle through a different mechanism than that used for vesicles of the recycling pool. A long stretch of membrane, including the membrane from many vesicles, is taken up through **bulk endocytosis**, a process that takes minutes to complete. Once internalized, the membrane enters cisternae and then eventually is recycled into new and fresh synaptic vesicles either directly or via endosomes. Thus, two major routes exist for recycling vesicles:

- Clathrin-coated membrane from an individual vesicle of the recycling pool is endocytosed and forms a new vesicle in a matter of seconds.

- Membrane from numerous vesicles of the reserve pool are bulk endocytosed and bud off from intracellular storage organelles into numerous vesicles, a process that requires tens of minutes.

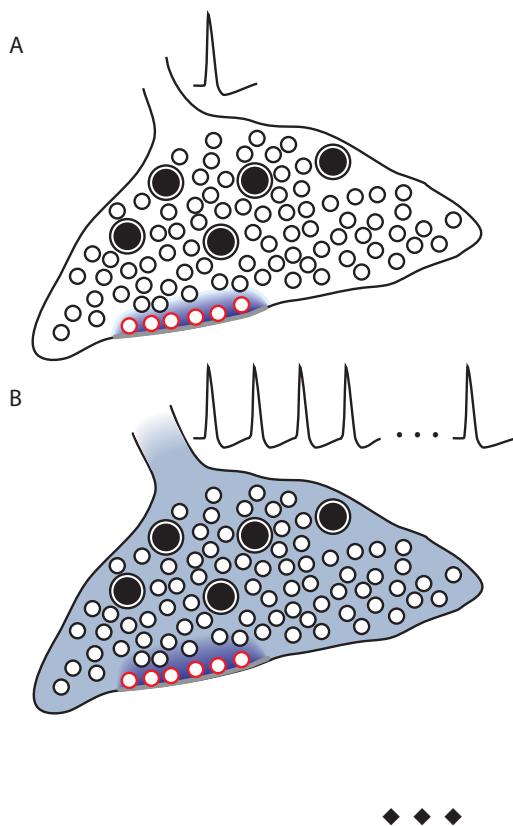
Within relatively inactive synaptic terminals that release only one or a few vesicles rarely, the number of docked vesicles is far less than the number in highly active synaptic terminals. Accordingly, the structure of the active zone varies to accommodate the docking of anywhere from a few to many vesicles. The presynaptic density often appears as an extension of the membrane into the cytosol. In a number of specialized sensory cells with high rates of neurotransmitter release, a **ribbon** extends into the cytosol with synaptic vesicles docked on all sides of the ribbon. Ribbon-containing synapses are present in sound- and light-sensing cells, as well as in vestibular sensory cells that respond to accelerating forces.

LARGE DENSE-CORE VESICLES ARE RELEASED USING DISTINCT MECHANISMS

Small vesicles containing low-molecular-weight neurotransmitters make up the readily releasable pool of synaptic vesicles packed around the active zone, as well as recyclable and reserve pools. As discussed above, a highly localized concentration of calcium ions confined to the active zone is sufficient for the fusion of small vesicles and consequent release of low-molecular-weight neurotransmitters. Remember that calcium channels crowd the active zone. Therefore, a local elevation of calcium ion concentration at the active zone can be achieved by the invasion of *a single action potential*.

No readily releasable pool of large, dense-core vesicles exists. Rather, large vesicles are scattered throughout the synaptic terminal, typically in locations relatively far from the active zone (Fig. 6-7). The fusion of large vesicles is only triggered when the concentration of calcium ions rises at the locations of the vesicles dispersed throughout the cytosol of the synaptic terminal (Fig. 6-7). Although the calcium ion concentration required for large-vesicle fusion is quite a bit lower than that needed for small-vesicle release, that concentration must be achieved globally within the terminal. Therefore, release from large vesicles typically requires a high-frequency train of action potential firing to achieve the needed calcium ion concentration throughout the synaptic terminal. In sum, *single action potentials preferentially release small vesicles containing low-molecular-weight neurotransmitters, whereas it often takes a train of action potentials to release large vesicles containing a mixture of peptides and low-molecular-weight neurotransmitters*.

Figure 6-7 Some synaptic terminals contain both small, clear vesicles and large, dense-core vesicles. As illustrated here, the number of small vesicles is usually much greater than the number of large vesicles. **A:** Readily releasable small vesicles (red circles) can fuse to the plasma membrane when the calcium ion concentration increases locally (dark blue cloud). A single action potential is capable of increasing the local calcium ion concentration and thus of triggering fusion of a small synaptic vesicle. **B:** In contrast, large, dense-core vesicles only fuse when the calcium ion concentration increases throughout the synaptic terminal (light blue). The calcium ion concentration needed to trigger dense-core vesicle fusion is far lower (B) than is needed for fusion of clear vesicles (A). Yet, a train of high-frequency action potentials is typically needed to produce this increase in calcium ion concentration *globally* throughout the terminal. Even as a train of action potentials produces a small increase globally, it also greatly increases calcium ion concentration locally at the active zone.



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CHAPTER 7

SYNTHESIS, PACKAGING, AND TERMINATION OF NEUROTRANSMITTERS

Neurotransmitters comprise a set of molecules that are heterogeneous in chemical structure, stability, and mode of action. Some neurotransmitters, such as glutamate and adenosine triphosphate (ATP), are present in all cells of the nervous system and body. Numerous other neurotransmitters, such as serotonin and the peptide neurotransmitters, are far more concentrated in non-nervous tissue than in neurons and glia. Thus, *neurotransmitters are not a special set of biological molecules dedicated to neural communication but rather a diverse group of molecules serving multiple duties in various tissues of the body, including the nervous system.*

By most estimates, there are more than hundred different neurotransmitters. This estimate is liberal in that the classic criteria for a neurotransmitter—that a substance is synthesized, present, and released from a terminal—have not been rigorously proven for every candidate neurotransmitter.

NEUROTRANSMITTERS DIFFER IN THEIR DISTRIBUTION, UBIQUITY, AND FUNCTION

The effect of neurotransmitters is extremely heterogeneous, with some participating in a myriad of functions and others in only a few. Examples of the multifunctional extreme are γ -aminobutyric acid (GABA) and glutamate, each of which participates in arguably every circuit within the central nervous system (CNS). Glutamate is a critical player in cellular learning regardless of whether the neurons participate in learning to ride a bike, speak a new language, recognize a new acquaintance, or solve a quadratic equation. Although the shared function of GABA is less clear, it appears to be important in accentuating differences, such as the edge of a visual object or the pause between spoken words. At the other extreme, some neurotransmitters participate in a relatively small number of functions.

Histamine, a major signalling molecule in the immune system that is released from mast cells, is present in neurons of a *single* brain nucleus that coordinates brain function with sleep–wake status. Another example is the peptide **growth hormone releasing hormone** or **GHRH**, which, like histamine, is synthesized by only one small group of hypothalamic neurons. As its name suggests, GHRH stimulates **growth hormone** release from the pituitary. In addition, GHRH-containing neurons project to other hypothalamic regions and thereby influence homeostatic functions.

Most neurotransmitters occupy a middle ground between these extremes, serving several, sometimes related but often unrelated, functions. As an example of one such neurotransmitter, consider the neuropeptide substance P. Substance P is contained within cutaneous nociceptors (neurons that code for superficial pain), and its release within the dorsal horn provides an important signal in pain transmission. Substance P is also contained in afferents from the stomach that trigger vomiting, or **emesis**, through actions in the brainstem, and in neurons of the striatum, substantia nigra, amygdala, and a number of other regions where the peptide's functions are varied.

NEUROTRANSMITTERS SHARE A RESTRICTED NUMBER OF MECHANISMS FOR SYNTHESIS, PACKAGING, AND TERMINATION OF EFFECT

Despite their extreme heterogeneity, neurotransmitters can be divided into three classes with different fundamental modes of synthesis, packaging, and action:

1. A dozen or so low-molecular-weight molecules comprise the so-called classical neurotransmitters that can be further subdivided into five subclasses:
 - a. Acetylcholine
 - b. Monoamines, which include serotonin, **dopamine**, **norepinephrine**, **epinephrine**, and histamine
 - c. Glutamate
 - d. GABA and **glycine**
 - e. Purines, such as ATP
2. There are *more than a hundred* small peptides, including but not limited to opioid peptides (e.g., **enkephalin** and **β-endorphin**), **vasopressin**, **oxytocin**, substance P, **calcitonin gene-related peptide** (**CGRP**), **somatostatin**, **bombesin**, **insulin**, **galanin**, **luteinizing hormone-releasing hormone** (**LHRH**), and **vasoactive intestinal protein** or **VIP**.
3. At least two gases, **nitric oxide** (**NO**) and **carbon monoxide** (**CO**), exist in solution and act as neurotransmitters.

Within each neurotransmitter class, individual neurotransmitters share similar modes of synthesis, packaging, and release and similar receptor type–activated mechanisms of termination of neurotransmitter action. The similarities within the three major groups are outlined in Table 7-1 and described in the following sections.

NEUROTRANSMITTER SYNTHESIS OCCURS LOCALLY EXCEPT IN THE CASE OF PEPTIDES

Low-molecular-weight neurotransmitters are mostly synthesized locally, and gases are always synthesized locally. Peptides, like other proteins, are synthesized in the cell body. For low-molecular-weight molecules, local production usually means synthesis within the synaptic terminal from where they are released. In contrast, as we shall see, gaseous neurotransmitters are often synthesized in a dendrite or dendritic spine (see Chapter 8).

Universally, enzyme activity depends on the concentrations of substrate and product (termed the **law of mass action**), the availability of co-factors, modifications such as phosphorylation of the enzyme, and the presence of enzyme inhibitors and activators. The dependence of enzyme activity on the concentrations of substrate and product is critical to understanding neurotransmitter synthesis in the nervous system. When more substrate is available, more transmitter is made, whereas when the neurotransmitter, the product, is present in abundance, the rate of synthesis decreases. Therefore, one important modulator of the activity of many neurotransmitter-synthesizing enzymes is neural activity. Typically, increased neural activity increases

TABLE 7-1. FUNDAMENTAL PROPERTIES SHARED BY MOST OR ALL MEMBERS OF THE THREE NEUROTRANSMITTER CLASSES ARE LISTED

	LOW-MOLECULAR-WEIGHT MOLECULES	PEPTIDES	GASES
Synthesis	Mostly in the terminal	In the soma	Locally, at the site of release
Packaging	In either small clear vesicles or large dense-core vesicles	In large dense-core vesicles	No packaging
Release trigger, location	Ca ²⁺ -dependent, single action potentials, from active zones	Ca ²⁺ -dependent, trains of action potentials, from perisynaptic regions outside the active zones	Ca ²⁺ -dependent, gas in solution diffuses directly upon synthesis
Effect	Activates ionotropic and metabotropic receptors, located both synaptically and perisynaptically	Activates metabotropic receptors located perisynaptically	Increases second messenger production and, in the case of NO, S-nitrosylates numerous protein targets
Termination of action	Diffusion, uptake, and/or enzymatic degradation	Diffusion and proteolysis	Diffusion and spontaneous degradation due to inherent instability and reactivity

the production of neurotransmitter by any number of modifications, such as increasing the activity of the synthesizing enzymes or the affinity of the enzymes for a co-factor or by decreasing the affinity of an enzyme for an inhibitor. Regardless of the mechanism, linking the rate of neurotransmitter synthesis to neurotransmitter release provides a mechanism that works to keep the supply of neurotransmitter in line with demand.

NEUROTRANSMITTERS ARE PACKAGED INTO VESICLES, EXCEPT IN THE CASE OF GASES

Although no physical property distinguishes the set of molecules that serves neural communication, and any given molecule may serve multiple roles in the body, *only hormones and neurotransmitters are packaged into vesicles*. Neurotransmitters fill vesicles at high concentrations, as much as one molar, relative to the surrounding cytosol, concentrations far exceeding those of the same molecules elsewhere in the body.

Within the synaptic terminal, low-molecular-weight molecule neurotransmitters are packed into vesicles using **vesicular transporters** that shuttle synthesized neurotransmitter from the cytosol into the vesicle. All low-molecular-weight neurotransmitters are packaged by one of only five types of vesicular transporters:

- **Acetylcholine transporter**, abbreviated as **VACHT** for vesicular acetylcholine transporter
- **Monoamine transporter**, abbreviated as **VMAT** for vesicular monoamine transporter
- **Glutamate transporter**, abbreviated as **VGLUT** for vesicular glutamate transporter
- **GABA and glycine transporter**, abbreviated as **VIAAT** for vesicular inhibitory amino acid transporter
- **ATP transporter**, abbreviated as **VNUT** for vesicular nucleotide transporter

All vesicles house an ATPase, an ATP-fueled pump, that uses cytosolic ATP to transport protons from the cytosol to the inside of the vesicle. As a result, *all synaptic vesicles have a high proton concentration. The proton gradient—low in the cytosol to high in the vesicle—is then used by the vesicular transporters to “load” neurotransmitter into the vesicle*. ATP is also present in high concentrations within most vesicles, including vesicles containing other, non-nucleotide neurotransmitters.

Peptides are packed into synaptic vesicles within the cell body where they are synthesized. Within the same vesicle that contains any given peptide, other peptides are often present, and vesicular transporters may be contained in the vesicle membrane. Synaptic vesicles reach the terminal through axonal transport (see Chapter 2), an active process through which vesicles are moved along the length of the axon in

an anterograde direction, from the cell body to the terminal. Within the synaptic terminals, vesicular transporters pack low-molecular-weight molecule neurotransmitters into the secretory synaptic vesicles. Note that gases are exceptions to the rule that neurotransmitters are packaged within vesicles. Gases are released directly from the cytosol where they are synthesized.

THE EFFECT OF NEUROTRANSMITTERS IS TERMINATED BY UPTAKE, DEGRADATION, AND DIFFUSION

As detailed in Chapter 6, synaptic vesicles, of both the small and large varieties, fuse to the membrane of synaptic terminals, allowing neurotransmitters to diffuse out. The release of neurotransmitters is clearly important. Yet, in order for it to be meaningful, *neurotransmitter release must have an end as well as a beginning*. An interminable message, like an interminable lecture, loses meaning. As described in Chapter 6, the start of neurotransmitter release is highly regulated, so that it starts synchronously upon the influx of calcium ions. The end is also regulated in several ways that are understood and in some ways that warrant further investigation.

A major contributor to both the onset and termination of a neurotransmitter's action is diffusion. Neurotransmitter diffuses from the site of release to the site of the receptor to which the neurotransmitter binds. At a typical synapse in the CNS, the **synaptic cleft** across which a neurotransmitter diffuses to reach the postsynaptic cell is narrow, about 30 nanometers across, whereas at the neuromuscular junction, the synaptic cleft is 100 nanometers wide. At other synapses, no classic synaptic cleft exists, and the location of the receptors may be some distance from the site of release. In still other cases, perhaps the majority of central synapses, neurotransmitter acts on receptors located both near and far from the site of release. As a result of diffusion, neurotransmitter concentration and thus the probability of a neurotransmitter's binding to a receptor decreases rapidly as one moves away from the site of release. In this way, *diffusion contributes enormously to terminating the message of every neurotransmitter*.

A set of transporters present in cellular membranes takes neurotransmitter from the extracellular space to the inside of a neuron or glial cell. This recycling process is termed **uptake** and effectively ends the action of many neurotransmitters, including most of the low-molecular-weight neurotransmitters. For other neurotransmitters, notably acetylcholine, extracellularly located enzymes break down excess neurotransmitter, thereby ending the synaptic message. Peptides diffuse away from the site of release and are degraded by extracellular peptidases. Gases diffuse away and, because of their inherent reactivity, have short half-lives.

Uptake and degradation are processes upon which many drugs act. The most prevalent psychotropic therapeutics, as well as the most widely abused drugs, act on transporters responsible for neurotransmitter uptake. Other therapeutics, as well as toxins, including pesticides and biological weapons, disable enzymes that degrade

neurotransmitters. In addition, a number of mutations in uptake transporters are associated with personality traits such as impulsiveness or aggression.

LOW-MOLECULAR-WEIGHT NEUROTRANSMITTERS ARE THE WORKHORSES OF THE NERVOUS SYSTEM

Most neurons use chemical transmission, and at most chemical synapses at least one low-molecular-weight neurotransmitter is released. Four low-molecular-weight neurotransmitters—glutamate, GABA, acetylcholine, and norepinephrine—are particularly abundant, with one of these four used as a neurotransmitter in virtually all peripheral and central neurons. In contrast, any one peptide may be employed by only a small number of neurons. Similarly, gases are far from ubiquitous.

As mentioned above, low-molecular-weight neurotransmitters are concentrated within vesicles using one of five transporter systems. We use the same five categories to divide up the neurotransmitters themselves:

- Acetylcholine
- Monoamines: three catecholamines (dopamine, norepinephrine, epinephrine), an indoleamine (serotonin), and an imidazoline (histamine)
- Excitatory amino acid: glutamate
- Inhibitory amino acids: GABA, glycine
- Nucleotides: ATP, adenosine

Box 7-1

NEURONS IN THE BASAL FOREBRAIN PROVIDE CHOLINERGIC INNERVATION TO THE TELENCEPHALON.

The basal forebrain is located ventral to the striatum at the anterior base of the telencephalon. Neurons in the basal forebrain use acetylcholine as a neurotransmitter and have widespread projections throughout the telencephalon. The release of acetylcholine from neurons in the basal forebrain facilitates many forms of learning.

Acetylcholine is the neurotransmitter released by all somatic motoneurons, as well as by all preganglionic autonomic motor neurons. In addition, acetylcholine is found in somata in a restricted number of brain regions such as the **basal forebrain** (see Box 7-1). A relatively small number of **cholinergic**, or acetylcholine-containing, neurons in selected brain regions have widespread axonal projections that reach throughout the brain and spinal cord. Similarly, a relatively small number of **monoaminergic** neurons, neurons containing a monoamine transmitter, project extensively throughout the CNS. For example, **histaminergic**, or histamine-containing, neurons are contained within a single hypothalamic nucleus, the **tuberomammillary nucleus**, but reach all parts of the brain and spinal cord through widely projecting axons. Centrally, histamine promotes wakefulness, and histamine receptor antagonists cause drowsiness. Dopamine, norepinephrine, and serotonin are monoamines that critically modulate virtually every function of the CNS from thermoregulation to muscle tone and posture to sleep-wake cycling, motivation, and affect. These transmitters will be discussed at greater length below. Epinephrine, an important hormone released by the **adrenal medulla**, is found in restricted sites

Box 7-2

DIMINUTION OF CHOLINERGIC TRANSMISSION IN THE FOREBRAIN CONTRIBUTES TO THE DEVELOPMENT OF DEMENTIA.

During normal aging, cholinergic neurons die, and this may contribute to the mild memory problems and other cognitive compromises that are common among the elderly. In contrast, individuals with Alzheimer's disease have a gross loss of cholinergic neurons, including those in the basal forebrain that innervate the cerebral cortex. Loss of cholinergic function contributes to the cognitive decline in Alzheimer's disease. **Anticholinesterase** drugs are drugs that slow the breakdown of acetylcholine (see more below). Anticholinesterase drugs are used to treat patients with Alzheimer's disease because they prolong the action of acetylcholine released from the remaining cholinergic neurons. These drugs do not address the underlying pathophysiology of Alzheimer's disease, nor do they miraculously improve cognitive function. However, they do delay symptoms in some people and improve function in fewer people. Thus, treatment with anticholinesterases represents one of the only hopes, modest though it may be, available to Alzheimer disease patients and their families.

within the CNS mostly having to do with homeostatic regulation of blood pressure, salt balance, and the like.

Glutamate is the most prevalent excitatory neurotransmitter in the brain. **Aspartate**, another amino acid, acts as an excitatory neurotransmitter in relatively few select regions of the brain. γ -Aminobutyric acid and glycine are inhibitory neurotransmitters, with GABA employed throughout the brain and spinal cord, and glycine used primarily in the spinal cord. As mentioned above, ATP is contained in all synaptic vesicles and thus is released from most, if not all, neurons. Yet, ATP is a particularly important signaling molecule at select synapses. Notably, ATP excites primary afferent synapses to signal sharp pain, as well as a full bladder. Adenosine, a purinergic nucleoside present in all cells, acts as an inhibitory neurotransmitter and may be important in promoting sleep. As most readers are personally aware, the adenosine receptor antagonist **caffeine** promotes wakefulness.

Space does not permit us to cover every neurotransmitter. Therefore, in the following sections, the synthetic pathway, vesicular packaging, and mode of termination of action for acetylcholine, three monoamines, glutamate, and GABA are described. We then consider peptide neurotransmitters as a group and nitric oxide as an example of the gaseous neurotransmitters.

ACETYLCHOLINE IS SYNTHESIZED IN THE NEURONAL TERMINAL AND RAPIDLY DEGRADED IN THE SYNAPTIC CLEFT

Acetylcholine is very important in the periphery, where it is the neurotransmitter used by all somatic motoneurons, preganglionic autonomic neurons, and postganglionic parasympathetic neurons. Acetylcholine is also an important neurotransmitter in the brain, where it serves as an important modulator for functions as wide ranging as attention, memory, and arousal state (see Box 7-2). Within the periphery, acetylcholine's critical role in movement and autonomic function and the easy access to the neuromuscular junction have facilitated detailed studies of acetylcholine synthesis, packaging, and degradation. As evidence of acetylcholine's critical role in movement and autonomic function, a number of naturally occurring diseases and toxins, as well as synthetic agents, target acetylcholine neurotransmission.

Choline acetyltransferase, an enzyme present in the cytosol of synaptic terminals, transfers the acetyl moiety from **acetyl coenzyme A** to **choline**, thereby resulting in acetylcholine (Fig. 7-1). Under normal circumstances, dietary intake is the source of choline, the substrate for choline acetyltransferase. Foods rich in choline include egg yolks, soy beans, and liver. The **choline transporter** within the plasma membrane of cholinergic terminals has a high affinity (see Box 7-3) for choline, transporting it from the extracellular space into neurons.

The vesicular acetylcholine transporter sits within the membrane of synaptic vesicles present in cholinergic terminals and transports acetylcholine into the

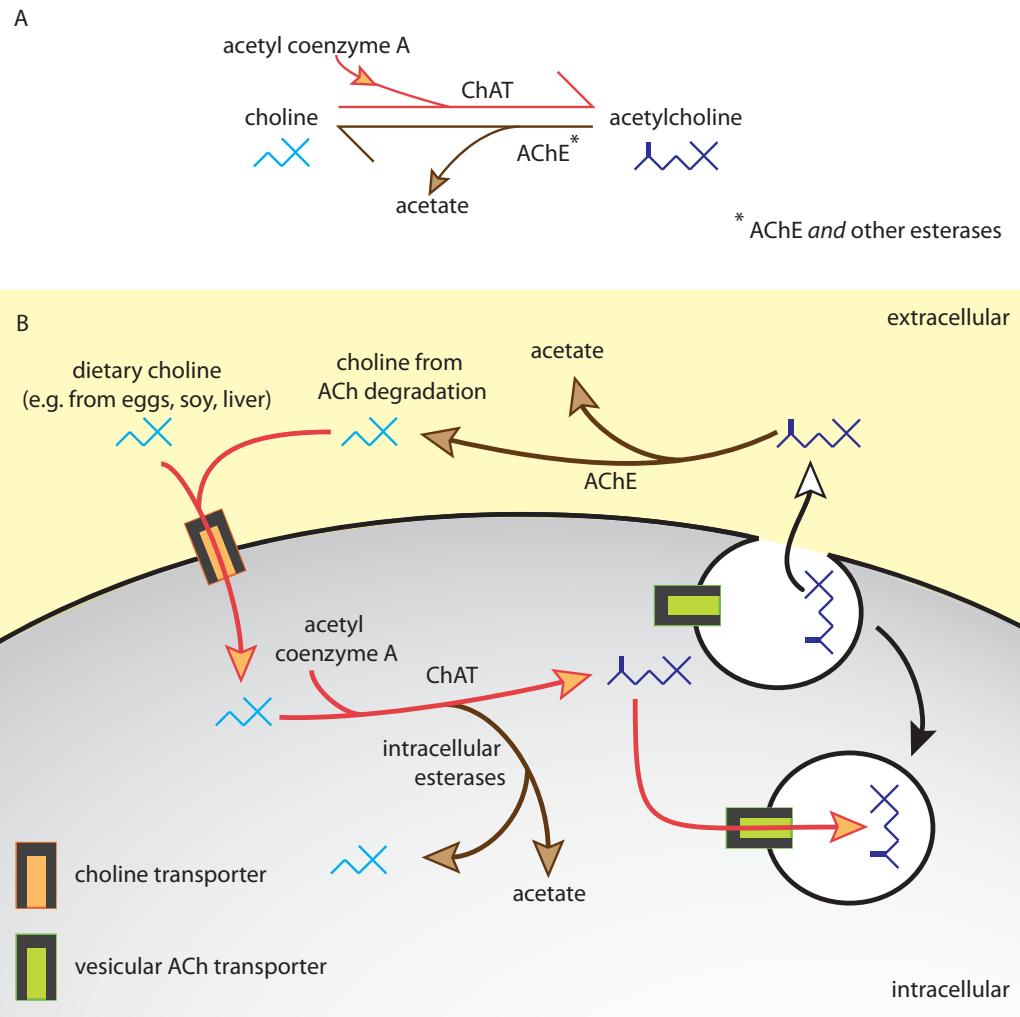


Figure 7-1. A: Acetylcholine is synthesized from choline and acetyl coenzyme A by choline acetyltransferase (ChAT). Acetylcholinesterase (AChE) and several other esterases break acetylcholine down into choline and acetate. B: The synthesis, packaging, release, breakdown, and uptake mechanisms involved in cholinergic transmission are illustrated *in situ*. Choline (light blue symbol as in A) from dietary sources and from the extracellular breakdown of released acetylcholine (dark blue symbol as in A) is taken up into cells by the choline transporter. Within cholinergic terminals, choline acetyltransferase catalyzes the synthesis of acetylcholine from choline and acetyl coenzyme A. The vesicular acetylcholine transporter shuttles ACh from the cytoplasm into synaptic vesicles. Upon release, acetylcholine is rapidly degraded by acetylcholinesterase. Within the terminal, esterases, including but not limited to acetylcholinesterase, break down acetylcholine.

Box 7-3

AFFINITY IS A PHARMACOLOGICAL TERM USED TO DESCRIBE THE INTERACTION BETWEEN TWO MOLECULES.

Receptors and transporters selectively bind to certain molecules more easily than to others. By easily, I mean that receptors and transporters bind

some molecules that are present at very low concentrations. This is a high-affinity interaction. In contrast, molecules with low affinity only bind to receptors or transporters when they are present at high concentrations.

Box 7-4

ACETYLCHOLINE CONCENTRATION RESULTS FROM BOTH CHOLINE ACETYLTRANSFERASE AND ESTERASE ACTIVITIES.

Acetylcholine production within the synaptic terminal follows the law of mass action, by which the rate of any reaction in dynamic equilibrium is proportional to the concentrations of the starting substrate and the end product. For example, a higher concentration of choline than of acetylcholine will favor acetylcholine production, whereas a higher concentration of acetylcholine than of choline favors acetylcholine degradation. In the case of acetylcholine *within neurons*, the situation is complicated because two enzymatic reactions are involved: choline acetyltransferase that produces acetylcholine and esterases that break it down. Acetylcholine is a substrate for esterases, as well as the end product of choline acetyltransferase, whereas choline is the substrate for choline acetyltransferase, as well as the end product of esterases. When acetylcholine builds up, choline acetyltransferase activity decreases and esterase activity increases, leading to a net breakdown of acetylcholine. In contrast, when choline builds up, choline acetyltransferase activity increases and esterase activity decreases, leading to a net synthesis of acetylcholine. In this way, large deviations in the concentration of acetylcholine away from equilibrium are prevented.

vesicles (Fig. 7-1). Acetylcholine turnover in the synaptic terminal is rapid, with the amount synthesized related by the law of mass action to the amounts of acetylcholine, product, and choline, substrate, present in the cytosol (see Box 7-4). As acetylcholine is transported into recycling vesicles, the free acetylcholine concentration decreases and production increases. **Esterases** are enzymes that break acetylcholine down into choline and acetate. **Acetylcholinesterase** is an esterase that is preferentially located extracellularly. Other esterases are preferentially present within cholinergic synaptic terminals.

After release into the synaptic cleft, acetylcholine is degraded *extremely rapidly* by a large pool of extracellular acetylcholinesterase (Fig. 7-1). Extracellular choline is taken up by a choline transporter in the synaptic terminal, providing the starting substrate for further synthesis of acetylcholine. A large number of drugs and toxins, ranging from efficacious therapeutics to insecticides to agents of biological warfare, interfere with acetylcholinesterase function (see Box 7-5).

MONOAMINES SHARE A COMMON PACKAGING MECHANISM

There are five monoamines: histamine, serotonin, dopamine, norepinephrine, and epinephrine (see Box 7-6). The monoamines depend on different synthetic pathways, and their actions are terminated by a variety of different mechanisms. Yet, they all share a requirement for the vesicular monoamine transporter, or VMAT, which transports histamine, serotonin, dopamine, and epinephrine, synthesized within the cytosol, into synaptic vesicles. An additional monoamine, norepinephrine, is synthesized within synaptic vesicles from dopamine transported into the vesicles by VMAT (Fig. 7-2). Because of their shared dependence on VMAT, the monoamines can be viewed as a single neurotransmitter class, albeit a highly heterogeneous one.

MONOAMINES ACT IN A HORMONE-LIKE FASHION, RATHER THAN AT CLASSICAL SYNAPSES

A second similarity shared by monoamines is the paucity of classical synapses, involving a presynaptic element and a postsynaptic element separated by a narrow synaptic cleft, associated with monoaminergic terminals. Instead, monoamines appear to depend primarily on **volume transmission**, meaning that monoamine neurotransmitters act at some distance from the site where they are released. Thus, the presynaptic monoaminergic release site is often simply a varicosity at some distance from the postsynaptic receptors where the released monoamine binds. By current estimates, monoamines travel up to 20 microns, a staggering distance, before decreasing to an ineffective concentration. Considering that a typical synaptic cleft is on the order of 30 nanometers across,

Box 7-5

ANTICHOLINESTERASES ARE IMPORTANT THERAPEUTICS AND ALSO LETHAL WEAPONS.

Anticholinesterases, drugs that interfere with acetylcholinesterase activity, prolong the effect of acetylcholine. Prolonging cholinergic signaling is therapeutic in conditions such as myasthenia gravis, in which cholinergic signaling is reduced. **Myasthenic** patients are weak because of a reduction in the number of acetylcholine receptors present on skeletal muscles (see Box 8-6). **Edrophonium**, a very short-acting anticholinesterase is used as a diagnostic tool: a patient with myasthenia gravis can sustain a stronger muscle contraction for a longer

time after edrophonium. Longer-acting, but still reversible, anticholinesterases such as **neostigmine** provide effective treatment for patients with myasthenia gravis. Insecticides such as **parathion** are irreversible anticholinesterases and, at sufficient doses, can kill humans as well as insects. Finally, agents designed to kill humans, such as **sarin**, are, like insecticides, irreversible anticholinesterases. Sarin is highly volatile and easily passes through the skin. Even minute amounts of sarin are lethal to humans.

Box 7-6

TWO CATECHOLAMINES GO BY DIFFERENT NAMES IN AMERICA AND EUROPE.

Norepinephrine is synonymous with **noradrenaline** and epinephrine with **adrenaline**. Customarily, Americans use norepinephrine and epinephrine, as I do in this book, whereas Europeans employ noradrenaline and adrenaline. Note that neurons that contain norepinephrine are referred to as **noradrenergic** and those that contain epinephrine are referred to as **adrenergic** in America and Europe alike. Similarly, receptors that bind norepinephrine and epinephrine are always referred to as **adrenergic receptors**.

the extracellular distance potentially traveled by monoamines is almost 1,000 times greater than the distance traversed by a neurotransmitter at a classical synapse. *The upshot of volume transmission is that monoamines released from one site act on a large number and variety of cells located anywhere within a large radius from the site of release.*

MONOAMINES ARE CRITICAL TO MOOD AND AFFECT

Of the five monoamines used as neurotransmitters, we focus here on serotonin, dopamine, and norepinephrine (see Box 7-7). These three neurotransmitters modulate virtually every brain pathway. As pharmacological manipulations of these transmitters consistently alter affect and mood, drugs that affect the synthesis and uptake of serotonin, dopamine, and norepinephrine are typically termed **psychotropic**. Psychotropic drugs affect psychological function, and are used to treat a number of psychiatric disorders.

Although many think that a decrease in serotonergic transmission leads to depression, an excess of serotonin to aggression, and so on, precise alignments between particular monoamine deficits and particular psychiatric disorders have eluded investigators to date. One reason for this difficulty is that many psychotropic drugs, such as those used to treat depression, must be taken for weeks before providing any relief, presumably because long-term changes in transmitter metabolism and receptor responsiveness are necessary for clinical efficacy. Further, although one monoamine *may* play a primary role in any given psychiatric disorder, serotonin, dopamine, and norepinephrine are all likely to contribute.

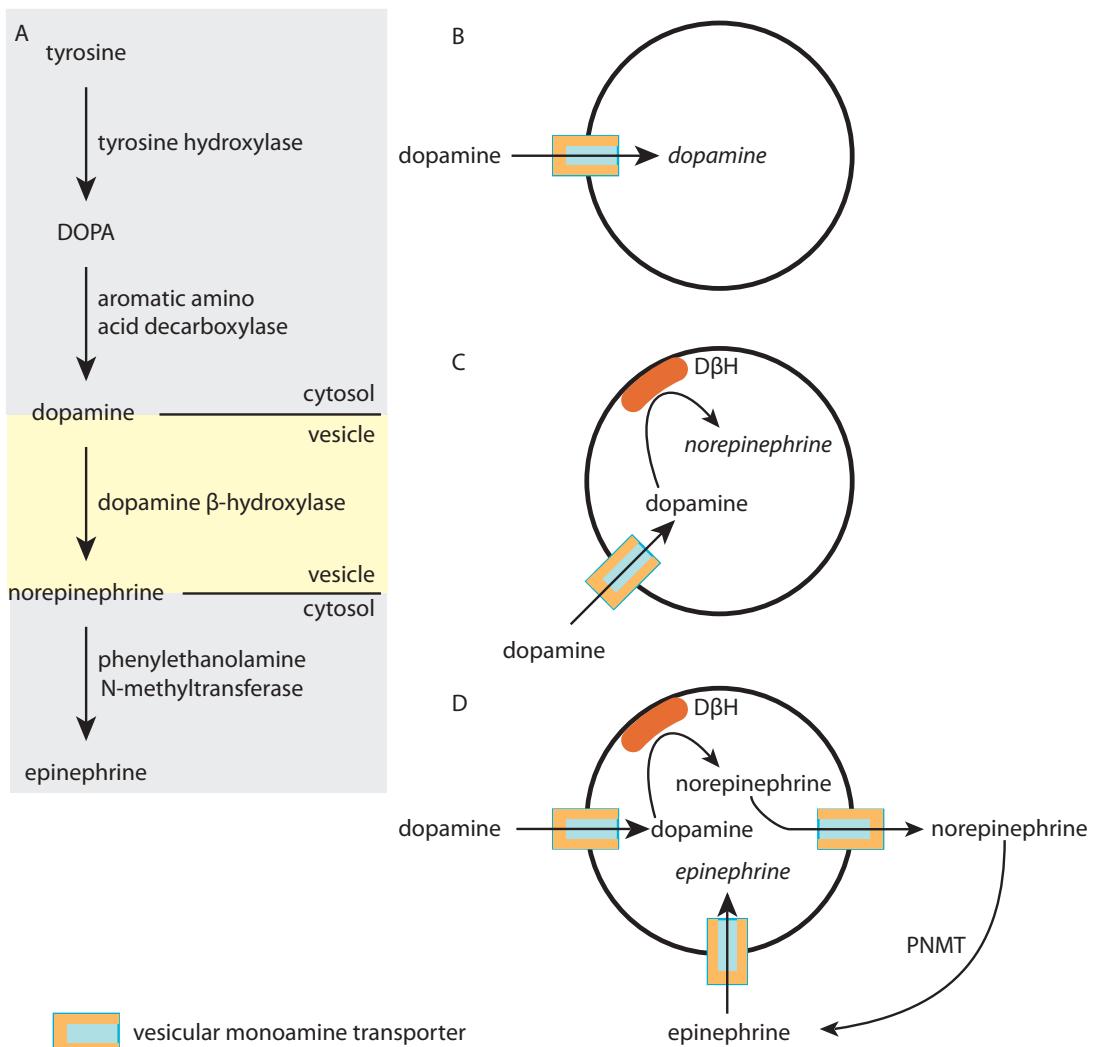


Figure 7-2. A: Tyrosine hydroxylase, the rate-limiting step in catecholamine synthesis, converts tyrosine into DOPA. Aromatic amino acid decarboxylase converts DOPA into dopamine, and dopamine β -hydroxylase converts dopamine into norepinephrine. Finally, phenylethanolamine N-methyltransferase converts norepinephrine into epinephrine. All of these reactions *except* the conversion of dopamine into norepinephrine take place in the cytoplasm, and this exceptional reaction takes place within the synaptic vesicle. B: In dopaminergic, or dopamine-containing, terminals, the vesicular monoamine transporter transports dopamine, made in the cytoplasm, into synaptic vesicles. Neither dopamine β -hydroxylase nor phenylethanolamine N-methyltransferase are found in dopaminergic terminals. C: In noradrenergic, or norepinephrine-containing, terminals, the vesicular monoamine transporter transports dopamine, made in the cytoplasm, into synaptic vesicles and dopamine β -hydroxylase (D β H), present in the vesicle, then converts dopamine into norepinephrine within the synaptic vesicle. Phenylethanolamine N-methyltransferase is not present in noradrenergic terminals. D: The adrenergic terminal builds upon the noradrenergic terminal by *reverse* transporting norepinephrine out of the synaptic vesicle and into the cytoplasm. Phenylethanolamine N-methyltransferase (PNMT) then converts norepinephrine into epinephrine within the cytoplasm. Cytosolic epinephrine is transported into the synaptic vesicle by the vesicular monoamine transporter. Note that adrenergic, or epinephrine-containing, terminals contain all of the catecholaminergic enzymes. B-D: The dominant neurotransmitter in the synaptic vesicle is shown in *italics*. In dopaminergic terminals (B), only dopamine is synthesized and transported into vesicles. However, in noradrenergic terminals (C), norepinephrine predominates but lesser amounts of dopamine are present. Similarly, in adrenergic vesicles (D), some dopamine and norepinephrine are present along with mostly epinephrine.

Box 7-7

WE GIVE SHORT SHRIFT TO EPINEPHRINE WITH SOME CAUTION.

In cautioning against making short shrift of the importance of central epinephrine, Arvid Carlsson, winner of the Nobel Prize in 2000 for studies on dopamine and Parkinson's disease, said "we have to take into account the fact that the brain is not a democracy," adding, "that is perhaps the reason why it works so well most of the time" (Fuller, 1982). Epinephrine-containing neurons are contained in both the brainstem and hypothalamus and appear to be important for cardiovascular regulation, as well as for other homeostatic functions. Although brain epinephrine systems are not as well studied as dopaminergic and noradrenergic ones, they may nonetheless play as of yet unheralded and critical roles.

CATECHOLAMINES SHARE SYNTHETIC AND PACKAGING STEPS BUT HAVE DISTINCT UPTAKE MECHANISMS

A series of synthetic steps leads to the formation of the three catecholamine neurotransmitters. Two steps convert **tyrosine** (see Box 7-8) to dopamine, which is then the substrate from which norepinephrine is synthesized, which in turn can be converted to epinephrine (Fig. 7-2A). The first step in making any catecholamine is the conversion of tyrosine into L-3,4-dihydroxy-L-phenylalanine or **DOPA** by **tyrosine hydroxylase**. **Aromatic amino acid decarboxylase** or **AAAD** then converts DOPA, often called **L-DOPA**, into dopamine. The two-step process from tyrosine to dopamine occurs entirely in the cytosol of synaptic terminals. VMAT transports available dopamine into synaptic vesicles. For a neuron that releases dopamine, a **dopaminergic** neuron, the synthetic pathway is complete, and additional catecholaminergic enzymes are not present (Fig. 7-2B).

In **noradrenergic** neurons, those that synthesize and release norepinephrine, the enzyme **dopamine β -hydroxylase**, or **DBH**, converts dopamine contained *within a vesicle* into norepinephrine. Norepinephrine synthesized *in situ* within the vesicles is released upon appropriate stimulation (Fig. 7-2C). The pathway to epinephrine synthesis requires a strange-but-true step wherein norepinephrine is transported by VMAT *back out of the vesicles and into the cytosol!* Once in the cytosol, **phenylethanolamine N-methyltransferase**, or **PNMT**, methylates the amine group of norepinephrine to form epinephrine. Cytosolic epinephrine is transported into synaptic vesicles by VMAT (Fig. 7-2D). It may seem strange that norepinephrine is made in the vesicle rather than the cytosol and transported back out in epinephrine-synthesizing or **adrenergic** neurons. However, this odd detour allows a noradrenergic cell to package norepinephrine *preferentially* over dopamine; if norepinephrine were made in the cytosol along with dopamine, VMAT

Box 7-8

A DEFICIT IN TYROSINE SYNTHESIS CAUSES PHENYLKETONURIA.

Phenylalanine hydroxylase converts phenylalanine, an essential amino acid, into tyrosine, the amino acid that is the starting material for all catecholamine synthesis. Deleterious mutations in the gene for phenylalanine hydroxylase cause **phenylketonuria** commonly abbreviated as **PKU**. Although normally nonessential, tyrosine is an essential amino acid in individuals with PKU, who must take in tyrosine through diet. Due to their lack of phenylalanine hydroxylase, patients with PKU also accumulate

phenylalanine, which causes great harm. Left untreated, the accumulation of phenylalanine consequent to PKU severely impairs brain function, causing intellectual disability and other serious neurological consequences. Luckily, a genetic test applied via heel stick to babies born in hospitals can identify PKU cases immediately after birth. The adverse consequences of PKU can then be largely avoided by strict adherence to an appropriate diet.

would transport both monoamines into vesicles in comparable amounts. In fact, norepinephrine-containing vesicles also contain some dopamine and epinephrine-containing vesicles contain some norepinephrine, as well as some dopamine.

The type of catecholaminergic neurotransmitter used by a specific cell is determined by the synthetic enzymes present (Fig. 7-2A). Thus, neurons that contain tyrosine hydroxylase and aromatic amino acid decarboxylase but lack dopamine β -hydroxylase and phenylethanolamine N-methyltransferase synthesize dopamine. In contrast, cells that contain tyrosine hydroxylase, aromatic amino acid decarboxylase, and dopamine β -hydroxylase but not phenylethanolamine N-methyltransferase, make and release norepinephrine. Cells that contain all four enzymes are **adrenergic**, meaning that they make epinephrine.

Catecholaminergic synthesis is regulated and modulated at a myriad of points and by many factors. As with acetylcholine, the law of mass action applies. The more catecholamine product present, the less is synthesized, and the more substrate present, the more catecholamine is synthesized. The rate-limiting step in all catecholamine production is the very first enzymatic step converting tyrosine to DOPA. For this reason, providing DOPA to patients with Parkinson's disease, who have greatly reduced levels of dopamine, bypasses the bottleneck in catecholamine synthesis, thereby boosting the synthesis of all catecholamines including dopamine.

Two enzymes degrade catecholamines:

- Catechol-O-methyl transferase or COMT
- Monoamine oxidase A or MAO-A

Catechol-O-methyl transferase degrades catecholamines extracellularly and MAO-A does so within the presynaptic terminal. Although it would be natural to think that COMT inhibitors increase the time that catecholamines spend extracellularly, *catecholamine reuptake is so fast* that any effect of COMT inhibitors is minor. Increasing COMT activity, on the other hand, can have effects on catecholaminergic transmission (see Box 7-9).

Monamine oxidase-A is present on mitochondrial membranes within the presynaptic terminal where it strongly influences the synthesis of catecholamines. The relative activities of MAO-A on one hand and synthetic enzymes for monoamines on the other determine the presynaptic concentration of any catecholamine. When monoamine oxidase A is inhibited, by any of a number of clinically used **monoamine oxidase A inhibitors** (see Box 7-10), then the amount of catecholamine available for release increases. Until the advent of **tricyclic antidepressants** and subsequently **selective serotonin reuptake inhibitors (SSRIs)**, MAO-A inhibitors were often the first drug prescribed in cases of **clinical depression**.

In terms of mechanisms that enable a speedy termination of catecholamine action, catecholamine degradation pales in comparison to catecholamine reuptake via specific transporters. Dopamine and norepinephrine are taken up by **dopamine and norepinephrine transporters**, or **DATs** and **NETs**, respectively. Thus, although all catecholamines share a single vesicular transporter, they are taken up through different, more selective transporters present on the plasma membrane.

Box 7-9

VARIATIONS IN THE COMT GENE ARE ASSOCIATED WITH DIFFERENT PERSONALITY TRAITS.

Natural variations in the *COMT* gene across the human population are associated with different personality traits. One substitution, valine for methionine at codon 158, results in a *COMT* with far greater enzymatic activity than normal. It is thought that a large increase in *COMT* activity decreases the extracellular concentration of catecholamines available to postsynaptic receptors. People with the **val158met** variant of the *COMT* gene are more neurotic and less extroverted than those without this variant. This remarkable association between high-order behavior, indeed personality traits, and a single gene speaks to the importance of catecholamines in psychological function.

Box 7-10

GENETIC VARIATION IN THE GENE FOR MONOAMINE OXIDASE IS ASSOCIATED WITH ABNORMALITIES IN AGGRESSIVE BEHAVIOR.

A rare X chromosome mutation present in a Dutch family results in a complete absence of monoamine oxidase A activity. Men in this family exhibit a pathological and explosive form of aggression and impulsive destructive behavior. More commonly, naturally occurring mutations in the promoter or coding regions of the gene for monoamine oxidase result in a down-regulation of monoamine oxidase

or a decrease in the activity of monoamine oxidase. When coupled with adverse environmental conditions, mutations of both sorts are associated with psychiatric disorders marked by ballistic episodes of extreme aggression. Further, people with lower levels of monoamine oxidase activity tend to be more aggressive than those with higher levels.

Drugs that act upon dopamine and norepinephrine transporters include important therapeutics, as well as drugs of abuse (see Boxes 7-11 and 7-12).

SEROTONIN IS FORMED FROM TRYPTOPHAN BY TRYPTOPHAN HYDROXYLASE

Serotonin synthesis requires the essential amino acid **tryptophan**. To reach the CNS, tryptophan must be carried across the blood–brain barrier by the **large neutral amino acid carrier** that transports a number of amino acids—valine,

Box 7-11

TRICYCLICS WERE ORIGINALLY USED TO TREAT DEPRESSION AND NOW ARE USED TO TREAT OTHER CONDITIONS AS WELL.

Tricyclic antidepressants are minimally selective monoamine reuptake inhibitors that inhibit the transport of both norepinephrine and serotonin, through actions at the respective reuptake transporters. Inhibiting norepinephrine and serotonin reuptake results in high concentrations of norepinephrine and serotonin present extracellularly for a long time. However, the efficacy of tricyclic antidepressants in relieving depression is more likely due

to a long-term effect that is secondary to the increase in norepinephrine and serotonin, rather than to an acute increase in neurotransmitter levels. Since the advent of newer drugs for the treatment of depression, tricyclic antidepressants are less often prescribed for depression. Despite being termed *antidepressants*, these compounds are now often prescribed to provide relief to patients with certain types of chronic pain.

COCAINE AND AMPHETAMINE INHIBIT MONOAMINE REUPTAKE.

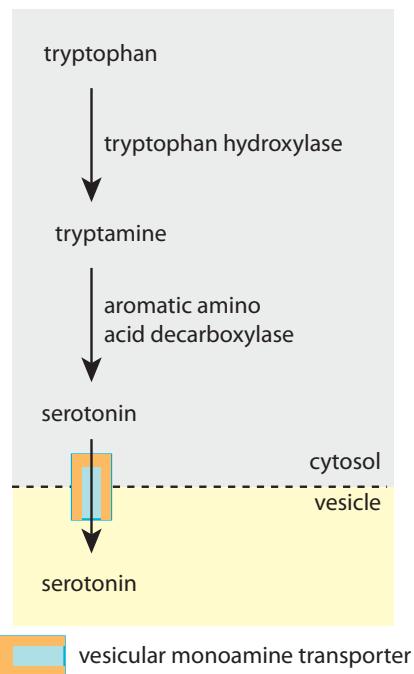
Cocaine is a nonselective monoamine reuptake inhibitor that inhibits the transport of dopamine, norepinephrine, and serotonin. The addictive nature of cocaine is thought to derive primarily from cocaine's effects on dopamine reuptake. With dopamine reuptake blocked, dopamine lingers at receptors for a longer than normal time. **Ampetamine**, another addicting substance, increases the concentration of dopamine in dopaminergic terminals through effects on both the vesicular monoamine transporter (VMAT) and the dopamine transporter (DAT). By acting on VMAT to reverse the direction of

dopamine transport, amphetamine results in the transport of dopamine from synaptic vesicles to the cytosol. Consequently, the concentration of intracellular dopamine increases to such an extent that DAT transports dopamine *from the cytosol to the extracellular space*. Although both cocaine and amphetamine greatly increase the dopamine present extracellularly, the actual mechanism of addiction for both of these substances is likely to depend on changes in receptor properties, as well as on increases in dopamine levels.

leucine, isoleucine, tyrosine, tryptophan, and other substances such as DOPA. Tryptophan competes with other possible substrates for transport across the blood–brain barrier by the large neutral amino acid carrier. Eating meals rich in carbohydrates and proteins increases serum tryptophan levels, which in turn increases brain tryptophan levels and *may* underlie a post prandial serotonin surge within the brain following a large meal of both carbohydrates and fish or meat.

Tryptophan hydroxylase is thought to have arisen by gene duplication of its close relative, tyrosine hydroxylase. Tryptophan hydroxylase converts tryptophan into **tryptamine** (Fig. 7-3). The same aromatic amino acid decarboxylase that converts

Figure 7-3. Tryptophan hydroxylase catalyzes the formation of tryptamine from tryptophan and is the rate-limiting step in the synthesis of serotonin. Aromatic amino acid decarboxylase, the same enzyme that converts DOPA into dopamine, decarboxylates tryptamine to form serotonin. Serotonin is transported into vesicles by the vesicular monoamine transporter, the same transporter that carries other catecholamines into vesicles.



Box 7-13

INDIVIDUALS WITH EATING DISORDERS AFFECT THEIR OWN SEROTONIN LEVELS THROUGH A RESTRICTED DIET.

People with eating disorders such as **anorexia nervosa** and **bulimia** restrict their own food intake, resulting in abnormally low levels of tryptophan. Oddly, supplemental tryptophan fails to restore tryptophan to normal levels in patients with anorexia nervosa. The decrease in serotonin levels consequent to less available tryptophan may contribute to the mood and affective traits associated with anorexia nervosa. Some evidence suggests that lowered serotonin levels may reduce anxiety in patients with anorexia nervosa, thereby serving as a type of self-medication.

DOPA into dopamine also decarboxylates tryptamine to give serotonin, which is **5-hydroxytryptamine**, or **5-HT**. As in the case of catecholamines, the first enzymatic reaction in the synthesis of serotonin is rate-limiting. In contrast to catecholamines, however, the supply of the initial amino acid substrate, in this case, tryptophan, is also a key determinant in how much serotonin is made. Dietary restriction of tryptophan intake impacts serotonin levels and alters brain function, whereas tryptophan loading increases serotonin synthesis (see Box 7-13).

The same VMAT that loads catecholamines and histamine into vesicles also transports serotonin into vesicles (Fig. 7-3). Once released extracellularly, serotonin is rapidly taken up by **serotonin transporters** or **SERTs**. Inhibitors that selectively inhibit SERT, such as **fluoxetine** and **sertraline**, increase the amount of serotonin in the extracellular space without affecting dopamine and norepinephrine uptake as much. Thus, this class of drugs, termed **specific serotonin reuptake inhibitors**, or **SSRIs**, can relieve depression in some people, while causing fewer side effects than do tricyclic antidepressants, which inhibit monoamine reuptake more broadly. Drugs that modify serotonergic transmission include drugs of abuse such as **MDMA** or **ecstasy**, as well as important therapeutics.

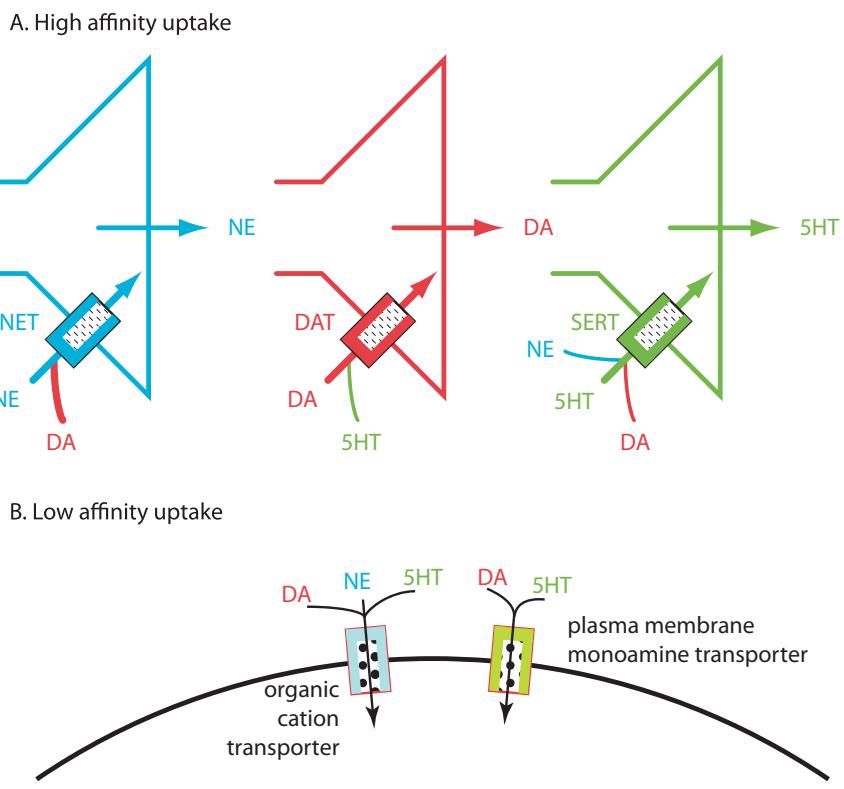
EACH MONOAMINE CAN BE TRANSPORTED BY A NUMBER OF MOLECULES

The names of the monoamine transporters—the norepinephrine transporter, the dopamine transporter, and the serotonin transporter—imply a specificity that does not reflect reality. In addition to transporting their eponymous neurotransmitter, the norepinephrine transporter transports dopamine, the dopamine transporter transports serotonin, and the serotonin transporter transports both norepinephrine and dopamine (Fig. 7-4). The situation is further complicated by the presence of two additional transporters:

- The **organic cation transporter** or **OCT** family transports norepinephrine, dopamine, serotonin, and histamine from the extracellular space into cells. The affinity for each monoamine differs across the OCT family members.
- The **plasma membrane monoamine transporter** or **PMAT** transports primarily dopamine and serotonin from the extracellular space into cells.

OCT and PMAT differ from the norepinephrine, dopamine, and serotonin transporters in that they have a low affinity for monoamines. However, since monoamines typically reach high concentrations, in the millimolar range, at release sites, they can diffuse long distances, up to 20 microns, before their concentration falls to a level that is below the affinity of OCT and PMAT. In essence, *OCT and PMAT act to mop up the excess monoamine in the extracellular space of the brain but they do so in a manner that is largely indiscriminate between the monoamines*. Such clearance of extracellular monoamines may account for the resistance of some individuals to the commonly

Figure 7-4. A: Synaptic terminals that release norepinephrine (blue NE, left), dopamine (red DA, middle), or serotonin (green 5HT, right) have a transporter with high affinity for the transmitter released. Yet, each of these transporters has some affinity for the other monoamines. The norepinephrine transporter (NET) has nearly equivalent affinity for dopamine as for norepinephrine. The dopamine transporter (DAT) has low affinity for serotonin in addition to high affinity for dopamine. Finally, the serotonin transporter (SERT) has low affinity for both dopamine and norepinephrine, as well as high affinity for serotonin. The high-affinity monoamine transporters are located perisynaptically, meaning near the synapse but not at the synaptic release site. Note that the synaptic terminals illustrated are cartoons of boutons. In reality, many monoaminergic release sites are varicosities. B: Two low-affinity transporters, the organic cation transporter and the plasma membrane monoamine transporter, are present on neighboring cells and contribute to the removal of monoamines from the extracellular space. Because of the high concentration of monoamines released, low-affinity uptake is effective even when located at some distance from the release site.



employed tricyclic antidepressants and SSRIs, particularly in individuals with an inherited down-regulation of the serotonin transporter (see Box 7-14).

NEURONS AND GLIA COOPERATE TO SYNTHESIZE GLUTAMATE

Glutamate, a nonessential amino acid, derives from diet or from one of at least two synthetic pathways. Neurons, like all cells, form glutamate when synthesizing either pyruvate or oxaloacetate from α -ketoglutarate, a key player in cellular metabolism (Fig. 7-5). Neurons also possess a neuron-specific synthetic pathway that utilizes mitochondrially located **glutaminase** to convert **glutamine** to glutamate. Once formed, glutamate is packaged into vesicles by the vesicular glutamate transporter.

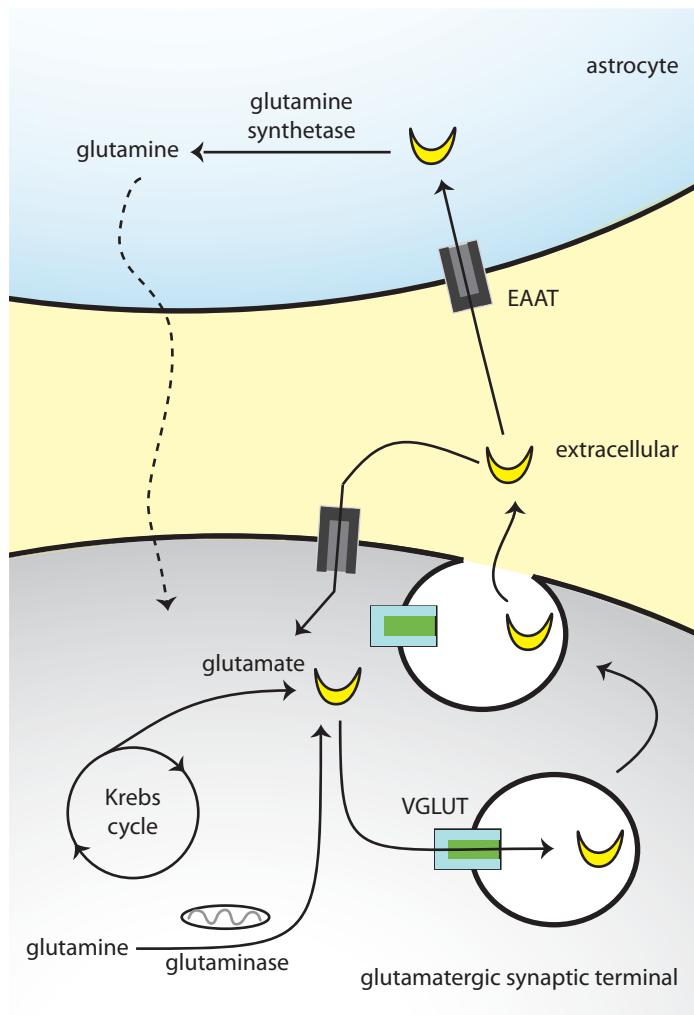
After glutamate release, **excitatory amino acid transporters** located in both neuron terminals and in surrounding astrocytes take up free glutamate (Fig. 7-5) with the energy derived by co-transporting sodium and potassium ions down their respective electrochemical gradients (see Box 7-15). Although most released glutamate appears to end up in glial cells rather than in neuronal terminals, excitatory amino acid transporters are present on synaptic terminals as well.

GENETIC VARIATIONS IN THE SEROTONIN TRANSPORTER (SERT) ARE ASSOCIATED WITH PERSONALITY TRAITS AND SUSCEPTIBILITY TO DEPRESSION.

Within the serotonin transporter promoter region, there is a polymorphism known as the **serotonin transporter-linked polymorphism** or **5HTTLPR**. The short allele of *5HTTLPR* decreases the amount of SERT made. Individuals with one or two copies of the short allele are more neurotic and less extroverted

than are those with the long allele. However, the short allele is only associated with major psychiatric disorders such as depression *if the carrier has experienced severe trauma*. This finding exemplifies the interplay between genes and environment in determining complex behaviors.

Figure 7-5. Astrocytes and neurons both participate in the synthesis, uptake, and degradation of glutamate (yellow symbol). Within synaptic terminals, glutamate is synthesized from glutamine by the mitochondrial enzyme, glutaminase. Glutamate is also one of the by-products of the Krebs cycle in all cells. Glutamate within synaptic terminals is transported into synaptic vesicles by the vesicular glutamate transporter (VGLUT), and after release, is taken up by both astrocytes and terminals through the excitatory amino acid transporter (EAAT). Within astrocytes, glutamate is converted into glutamine by glutamine synthetase. The molecules involved in transporting glutamine out of astrocytes and into terminals are not yet identified molecularly. Yet, glutamine does make it out of astrocytes and into neuronal terminals.



Box 7-15

GLUTAMATE UPTAKE IS PARTICULARLY CRUCIAL BECAUSE PROLONGED EXPOSURE TO GLUTAMATE IS TOXIC.

As discussed above, uptake of neurotransmitters, or some other mode of terminating transmitter action, is important in punctuating the message sent by neurotransmitter release. Rapid and efficient uptake of glutamate is *particularly* critical as prolonged exposure to glutamate causes **excitotoxicity** that ultimately results in the programmed cell death or **apoptosis** of neurons. When glutamate persists in the synaptic cleft, it sets in motion a series of events resulting in a large influx of calcium ions into the cell. A high intracellular concentration of calcium ions, in turn, triggers a number of deleterious events, including the activation of a variety of degradative enzymes. The excitotoxic effects of glutamate are most pronounced in neurons with the most calcium-permeable glutamate receptors (see Chapter 8) and with the weakest calcium-buffering capacity, features that mark hippocampal neurons. Thus, glutamate excitotoxicity preferentially damages neurons in the hippocampus, thereby disrupting new memory formation, at least temporarily. Excitotoxicity accompanies seizures, strokes, ischemic attacks, mechanical brain trauma, and apparently certain neurodegenerative diseases such as Huntington's disease. Finding therapeutics that mitigate the excitotoxic effects of glutamate is an active area of investigation.

The concentration of glutamine is higher, by at least ten-times, than any other amino acid both peripherally in blood and centrally in cerebrospinal fluid (CSF). Yet, negligible amounts of glutamine enter the brain from the blood. Instead, astrocytes produce glutamine, converted from glutamate by **glutamine synthetase**, within the brain, and thus are responsible for the high concentration of glutamine centrally. Because of the high concentration of glutamine, nearly one millimolar, in the extracellular fluid, neurons readily take up glutamine into synaptic terminals, using glutamine-specific transporters. Within the synaptic terminals, glutamine is converted to glutamate, which is then packaged into synaptic vesicles, completing the **glutamate-glutamine cycle** of synthesis, packaging, and release of glutamate by the neuron, and reuptake of glutamate and synthesis and release of glutamine by the astrocyte (Fig. 7-5).

GLUTAMATE IS THE SUBSTRATE FOR GABA SYNTHESIS

Glutamate, the most widely used excitatory neurotransmitter, is the substrate for synthesizing GABA, the most widely used inhibitory neurotransmitter. **Glutamic acid decarboxylase**, often abbreviated as **GAD**, converts glutamate into GABA (Fig. 7-6). γ -Aminobutyric acid is then packed into synaptic vesicles by the vesicular inhibitory amino acid transporter. This packaged GABA can then be released from the presynaptic terminal upon appropriate stimulation (see Box 7-16).

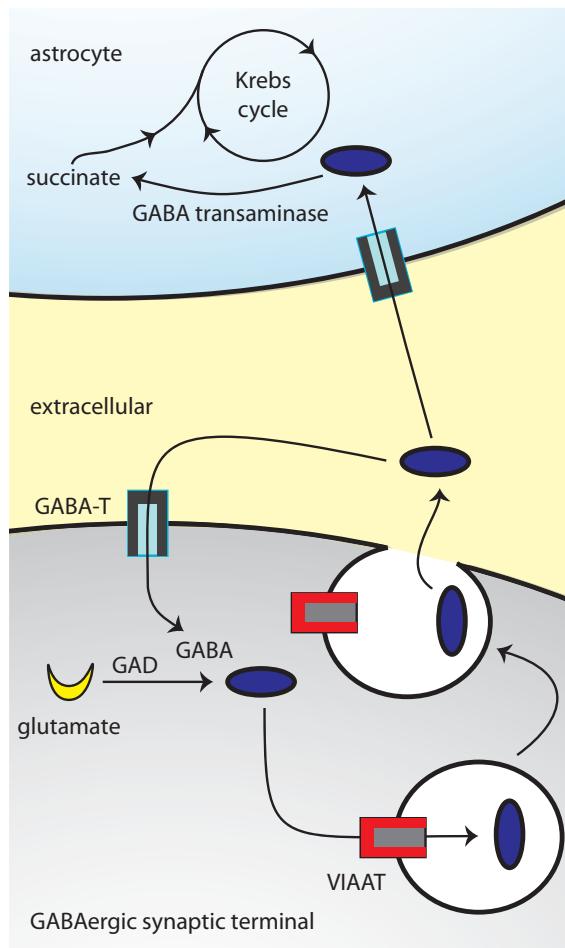
Extracellular GABA is taken up by **GABA transporters** present in the plasma membrane of both astrocytes and synaptic terminals. Within astrocytes, GABA is metabolized by **GABA transaminase** and ultimately returned to the Krebs cycle as succinate (Fig. 7-6). It should now be evident that the synthetic pathways of glutamate and GABA are highly inter-related (see Box 7-17).

PEPTIDES ARE DERIVED FROM LARGE PRECURSORS

Around 100 genes code for proteins that are processed into more than 100 peptide neurotransmitters. Peptides are short proteins, 3–80 amino acids in length, that are translated by ribosomes as larger pro-peptides and enzymatically processed to a mature, or released, peptide in the endoplasmic reticulum, Golgi apparatus, and vesicles. Once neuropeptide-containing vesicles—the large vesicle types—are transported to the synaptic terminal, the neuropeptides can be released by appropriate depolarization.

Neuropeptides are released from the synaptic terminal, far from the site of their synthesis and processing, in the cell body. Furthermore, neuropeptides are not recycled or taken up as are low-molecular-weight neurotransmitters. Instead, neuropeptides diffuse away from sites of release and eventually are degraded by

Figure 7-6. Astrocytes and neurons both participate in the synthesis, uptake, and degradation of γ -aminobutyric acid (GABA). GABA (blue oval) is formed from glutamate by glutamic acid decarboxylase (GAD) and then put into vesicles by the vesicular inhibitory amino acid transporter (VIAAT). After release, GABA is taken up by astrocytes and terminals by the GABA transporter (GABA-T). In synaptic terminals, GABA is recycled to fill synaptic vesicles anew, whereas in astrocytes, GABA is converted to succinate by GABA transaminase. Succinate is used in the Krebs cycle.



extracellular proteases. Since neuropeptides cannot be synthesized and repackaged in vesicles within the synaptic terminal, it is not surprising that the membrane of large, dense-core vesicles is also not recycled.

NITRIC OXIDE SERVES AS A RETROGRADE SIGNAL

Nitric oxide is formed from arginine and oxygen by **nitric oxide synthase** or **NOS**. Remember that gases in solution diffuse freely through intracellular and extracellular compartments and across membranes. Therefore, once synthesized, nitric oxide diffuses away, the gaseous equivalent of neurotransmitter release. In this way, synthesis and release are essentially a one step-process for gaseous neurotransmitters such as NO.

A common way of activating NOS is by the actions of calcium ions and **calmodulin**. Calmodulin is a calcium ion–binding protein that is ubiquitous in all cells. As the reader knows, calcium ion concentrations can be increased by opening voltage-gated channels (Chapter 4). As discussed in the next chapter, calcium ion concentrations can also be increased by opening ligand-gated channels. For example,

Box 7-16

IMPAIRMENT OF GLUTAMIC ACID DECARBOXYLASE PRODUCES A SYNDROME THAT INCLUDES INCREASED MUSCLE TONE, EPILEPSY, AND DIABETES MELLITUS.

Stiff-man syndrome, now correctly termed **stiff-person syndrome**, is a rare disease associated, in more than 80% of the cases, with the presence of antibodies to glutamic acid decarboxylase, the γ -aminobutyric acid (GABA)-synthesizing molecule employed by GABAergic inhibitory neurons. By interfering with GABA synthesis, errant antibodies lead to less GABA synthesis and then to less GABA-mediated, or **GABAergic**, inhibition, including less inhibition of motoneurons. Releasing motoneurons from inhibition is immediately apparent as an increase in muscle tone (see Section 5). The muscles of patients with stiff-person syndrome are both rock-hard and painful. Because stiff-person syndrome symptoms rarely progress to affect breathing, the disease is rarely fatal.

The reader may wonder why the symptoms of stiff-person syndrome and tetanus differ since both are associated with dysfunction of GABAergic neurons. Differences stem from two important dissimilarities in the pathophysiology. First, tetanus selectively affects a small subset of all GABAergic neurons, only those that directly synapse onto motoneurons, whereas all GABAergic neurons are impacted in stiff-person syndrome. Second, tetanus blocks all neurotransmitter release from GABAergic pre-motor neurons, whereas stiff-person syndrome

is associated with the failure of the synthetic pathway for GABA. Since neurons may release multiple neurotransmitters, a GABAergic neuron in a patient with stiff-person syndrome may continue to synthesize and release, for example, neuropeptides, a monoamine, or adenosine triphosphate (ATP).

Because all glutamic acid decarboxylase (GAD)-containing cells are affected in stiff-person syndrome, there are additional, nonmotor, and indeed non-neural, symptoms including:

- A high incidence of epilepsy, caused by a reduction in cortical inhibition
- Enhanced reactions to unexpected stimuli such as a tap on the shoulder, hearing a honking horn, or viewing a bolt of lightning, so that the patient freezes up and drops “like a log” to the ground
- Diabetes mellitus due to the GAD contained in insulin-producing pancreatic β cells

Patients with stiff-person syndrome are typically treated by a combination of immunotherapy, to suppress antibody formation, and sedating benzodiazepines, which facilitate transmission via the GABA_A receptor (see Chapter 8).

Box 7-17

PRIOR TO THE DEVELOPMENT OF ANTICONVULSANT DRUGS, A KETOGENIC DIET WAS USED TO TREAT EPILEPSY.

Prior to the advent of the first antiepileptic drug, **phenytoin**, a **ketogenic diet** was the primary method used to treat epilepsy. This diet, which in its modern form utilizes **medium-length triglycerides**, shifts the primary energy source from glucose to **ketone bodies**

derived from fat. The ketones reach the brain, where they reduce epileptic activity through mechanisms that remain unclear. One possibility is that ketones shift the balance from glutamate synthesis to γ -aminobutyric acid (GABA) synthesis by augmenting glutamine synthesis and inhibiting glutamate degradation, thereby forcing enhanced conversion of glutamate to GABA. Since following the ketogenic diet is very unpleasant, this therapeutic approach is currently restricted to patients with seizures that do not respond to pharmacological treatments such as phenytoin.

Box 7-18

FREE RADICALS ARE UNSTABLE, HIGHLY REACTIVE MOLECULES.

A free radical is a molecule with an unpaired electron in an orbit by itself. Unpaired electrons readily participate in chemical reactions, so that free radicals are unstable and short-lived.

calcium ion influx through a particular type of glutamate receptor activates NOS, in a calcium-/calmodulin-dependent fashion, resulting in the synthesis and release of NO. Flexibility in NO signaling is achieved through a number of modulatory points, including a handful of different potential co-factors, each of which can be modulated by other second-messengers, and through direct modulation of NOS activity. In this way, glutamate receptor activation can result in more or less NO released, depending upon the state of modulation.

The termination of NO signaling and its effects are still somewhat unclear. Clearly NO can diffuse throughout the tissue. Yet, as a free radical, NO has a short lifetime, just a few seconds, before it participates in a chemical reaction (see Box 7-18).

Nitric oxide is typically formed in the postsynaptic cell, and then diffuses in all directions, including retrogradely to the presynaptic terminal. Retrograde signaling is important because it provides an avenue for presynaptic terminals to receive information about the state of the postsynaptic target. In this way, presynaptic terminals can “find out” about changes, including damage, that occur in the postsynaptic target cells.

A VARIETY OF MOLECULES CAN HAVE NEUROTRANSMITTER-LIKE EFFECTS ON NEURONS

Some molecules that are not packaged and released as neurotransmitters nonetheless cause postsynaptic effects that are similar, and in some cases even indistinguishable, from the effects of neurotransmitters. For example, when mechanical trauma ruptures cell membranes, intracellular as well as membrane components are released into the extracellular space. In this way, large increases in the local concentration of glutamate, protons, ATP, arachidonic acid, and many other molecules and ions occur. All of the released substances can either activate postsynaptic receptors or modulate receptor activation by more traditional neurotransmitters. In the periphery, substances released from non-neuronal cells can also have neurotransmitter-like actions on peripheral neurons. Cytokines and histamine are released from various types of immune cells. Another source of neuroactive signaling molecules is blood. Substances such as bradykinin and serotonin, which are normally present in blood, may reach primary afferents after either rupture of a blood vessel or increased blood vessel permeability.



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CHAPTER 8

RECEIVING THE SYNAPTIC MESSAGE

To come full circle in understanding neural communication, we consider the process by which a neuron receives the messages that it then integrates and conducts to its own synaptic terminal. When a neuron or sensory cell releases transmitter, the electrical message conveyed by the transmitter depends on the complement of receptors present in the membrane of the cell receiving the message and the signaling molecules within that cell. Single neurotransmitters, such as acetylcholine, glutamate, serotonin, or norepinephrine, affect different target cells differently depending on the particular receptors and signaling molecules of the postsynaptic cell. Neurotransmitters bind to two fundamentally different types of receptor, leading to distinct outcomes:

- Binding to **ionotropic receptors** leads to the rapid opening of an ion channel.
- Binding to **metabotropic receptors** causes a conformational change in the receptor that, in turn, activates **guanine nucleotide-binding proteins**, or **G proteins**, as well as the receptor itself. *Activation of G proteins results in an enormous variety of slowly developing consequences* that can be broadly divided into two categories:
 - a. Changes in the electrical properties of a cell result when activated G proteins either directly affect ion channels or modify the activity of enzymes that synthesize **second-messengers** such as **cyclic AMP (cAMP)** or **inositol trisphosphate/diacylglycerol (IP₃/DAG)** which, in turn, affect ion channels, sometimes through the production of additional signaling molecules. Changes in electrical properties resulting from G protein-mediated affects on ion channels occur relatively slowly.
 - b. Electrically silent effects, such as changes in gene transcription, cytoskeletal structure, or another intracellular process mediated by second-messengers occur over the course of minutes, hours, or even days.

The fundamental differences between ionotropic and metabotropic receptors' functions stem from distinct physical structures (Fig. 8-1). *Ionotropic receptors are membrane protein complexes that both bind neurotransmitter and can undergo a conformational change that opens an ion-permeant pore that is part of the same complex.* Because *ionotropic receptors are also channels*, channel openings are very rapid, typically starting within a millisecond and continuing for only a few milliseconds.

In contrast to ionotropic receptors, *metabotropic receptors bind a ligand but do not themselves form an ion-permeant pore* (Fig. 8-1B). Instead *metabotropic receptors affect ion channels indirectly via G proteins*. As is the case with ionotropic receptors, metabotropic receptors that bind neurotransmitter change conformation. However, the conformational change of a metabotropic receptor does not result in pore formation but rather results in the activation of a G protein to which the receptor is bound on the intracellular side of the lipid bilayer. The G protein then acts either directly on an ion channel or on enzymes that synthesize second-messengers that themselves have a diversity of effects. As a result of these indirect mechanisms, metabotropic receptors cause changes in ion fluxes that are slower than those caused by neurotransmitter binding to ionotropic receptors.

The “adrenaline rush” familiar to everyone depends principally on the actions of adrenaline, typically termed epinephrine in the United States (see Chapter 7), on a

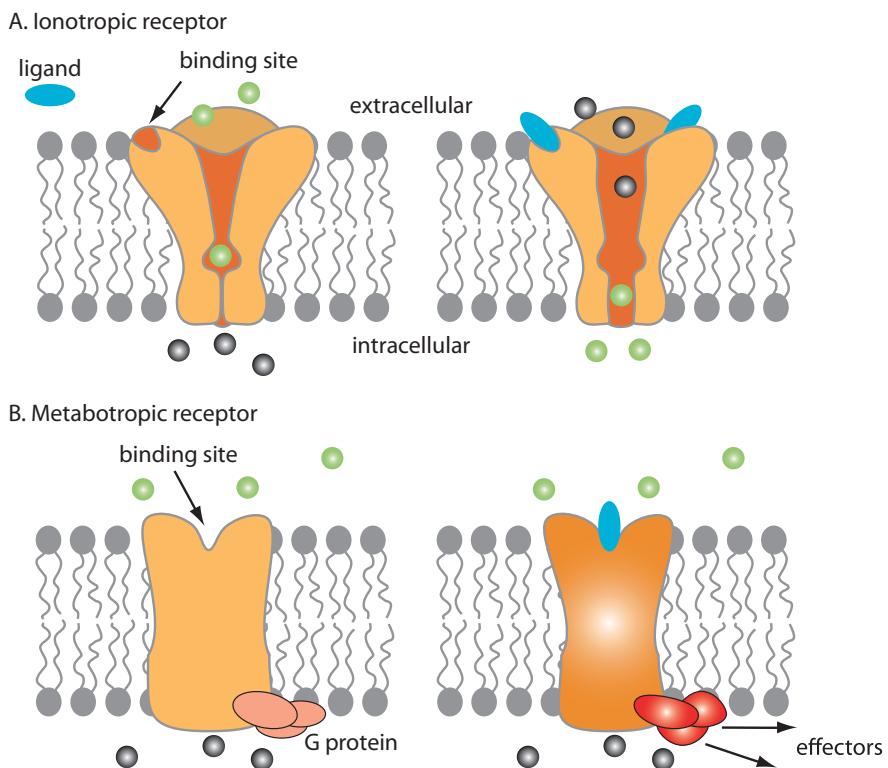


Figure 8-1. Different physical configurations underlie the functional properties of ionotropic (A) and metabotropic receptors (B). **A:** Ionotropic receptors form an open channel when bound to a neurotransmitter. Most ionotropic receptors require the binding of two neurotransmitter molecules (blue ovals marked ligand) for activation. The electrical consequences of ligand-binding to an ionotropic receptor are rapid and always involve channel opening that permits the passage of ions (green and black balls) through the channel pore. **B:** Metabotropic receptors are not able to form an open channel. When a neurotransmitter binds to a metabotropic receptor, the G protein that is bound to the receptor on the intracellular side becomes activated (right panel). The receptor itself also becomes activated. Metabotropic receptor and G protein activation can result in any number of effects through a variety of effector mechanisms. The critical point here is that metabotropic receptors only affect the electrical properties of a cell *indirectly*. No ions pass through a metabotropic receptor. Furthermore, metabotropic receptor activation can indirectly result in either the opening or closing of an ionotropic channel.

large number of peripheral targets, such as the heart and blood vessels, to increase heart rate and blood pressure. The onset of an adrenaline rush feels rapid but the time course of an adrenaline rush is in fact, measured in seconds to tens of seconds, orders of magnitude slower than the milliseconds that is the time scale of ionotropic receptor-mediated signaling. Furthermore, it is difficult to *turn off* the feeling of an adrenaline rush. The long-lasting time course of an adrenaline rush mirrors the kinetics of the metabotropic receptors that bind epinephrine in the periphery. In contrast, sensing the sting of a needle or jerking one's leg in response to a knee tap depends on fast ionotropic receptor-mediated transmission. In keeping with the time course of ionotropic receptor-mediated transmission, the pricking sensation and the knee jerk reflex begin and end very quickly.

We consider one other form of interneuronal communication, that mediated by gap junctions (see Chapter 4). Recall that gap junctions involve channels that actually connect the cytoplasms of two adjacent cells and allow ions and a number of small molecules, including second-messengers, to pass. Thus, gap junctions mediate rapid changes in membrane voltage as ions pass directly from one cell to another. They can also support slow changes in membrane voltage as second-messengers diffuse from one cell to another and subsequently alter the activity of ion channels, and even nutritive effects as metabolites travel between cells.

A LIMITED NUMBER OF IONOTROPIC RECEPTORS MEDIATE FAST SYNAPTIC TRANSMISSION

There are seven major ionotropic receptor types but well over a thousand metabotropic receptor types (see Box 8-1). Although relatively few varieties exist, ionotropic receptors are numerous in number. Moreover, ionotropic receptors are workhorses, mediating fast synaptic transmission at virtually all central synapses in the brain and spinal cord. In the periphery, motoneurons release acetylcholine, which acts on the prototypical ionotropic receptor, the **nicotinic acetylcholine receptor (nAChR)**, present in skeletal muscle, to excite skeletal muscle (see Box 8-2). Similarly, autonomic preganglionic neurons release acetylcholine, which acts on a different isoform of the nAChR to excite **ganglionic**, meaning of the *autonomic* ganglia, motor neurons. Although ionotropic receptors predominate in the central nervous system (CNS) and neuromuscular junction, acetylcholine and norepinephrine act exclusively on metabotropic receptors at the synapses between autonomic ganglionic motor neurons and target cells—cardiac muscle, smooth muscle, and glands.

When activated, most ionotropic receptors conduct, or allow passage of, monovalent cations, predominantly sodium and potassium ions, nonselectively. As we saw in Chapter 4, this depolarizes the cell toward a reversal potential of about zero millivolts. Two ionotropic receptors, the GABA_A and glycine receptors, pass chloride ions

THE NUMBER OF IONOTROPIC RECEPTORS IS LIMITED.

<u>Receptor</u>	<u>Endogenous ligand</u>
• nAChR*	acetylcholine
• AMPA	glutamate
• NMDA	glutamate
• GABA _A	GABA
• Glycine	glycine
• 5HT ₃	serotonin
• P2X	ATP

The seven major ionotropic receptors listed above can come in several different subtypes with distinct pharmacology, meaning that different drugs preferentially bind to and act at different subtypes. In addition to the major ionotropic receptors, there is at least one minor type of ionotropic receptor—a type of glutamate receptor preferentially activated by the ligand **kainate**. The kainate receptor, whose function is poorly understood, will not be discussed here.

A class of ionotropic receptors termed **transient receptor potential receptors**, or **TRP receptors**, warrants mention here. Several families of TRP receptors exist; these receptors are important to a number

of sensory **modalities**, meaning stimulus types. Transient receptor potential receptors contribute to thermosensation, chemosensation, and mechanosensation. Under natural circumstances, TRP receptors are activated by heat, cold, stretch, or chemicals released by cell rupture or damage (see much more on TRP receptors in Chapter 18 on somatosensation). For example, TRPV1 is activated by heat above 43°C or by protons, and is modulated by many of the products indicative of tissue damage. Furthermore, some, but not all, TRP receptors are either activated by or modulated by exogenous substances. In the case of TRPV1, capsaicin, the active ingredient that produces the pungency of hot peppers, is an agonist: when capsaicin binds to TRPV1, a cation pore opens. Other TRP receptors are activated or modulated by a number of compounds such as menthol, acrolein (a component of wood fire smoke and tobacco smoke), allyl isothiocyanate (the pungent ingredient in wasabi), and chlorine. Although the TRP receptors are clearly ionotropic receptors, we do not include them in this chapter because the ligands for TRP receptors are not neurotransmitters.

* Nicotinic acetylcholine receptor

primarily. The effect on membrane potential of increasing the permeability to chloride ions depends on the distribution of chloride ions inside and outside the cell. Since rest potential is usually a few millivolts more depolarized than E_{Cl^-} , opening GABA_A and glycine receptors at most adult synapses results in a hyperpolarization.

In the following sections, we consider the two glutamate receptors, the nAChR, and the GABA_A receptor in some depth. Although space does not permit discussion of the other ionotropic receptors, they too have important functions. The glycine receptor mediates inhibitory transmission, primarily in the spinal cord. Patients with certain mutations impacting glycinergic transmission, including several that are known to alter the glycine receptor itself, have an exuberant, nonhabituating **startle reflex**. The 5-hydroxytryptamine-3 (5-HT₃) receptor, present in nociceptors innervating the gut, and in many regions of the CNS, is an important mediator of nausea and vomiting. Thus, patients receiving nauseating therapeutics

Box 8-2

RECEPTORS ARE TYPICALLY NAMED FOR ONE OF THEIR LIGANDS.

Most receptors discovered prior to the 1990s are named after the natural ligand, as is the case for the glycine receptor, or after a particularly selective ligand. The latter is the case for the nicotinic acetylcholine receptor, which binds nicotine with moderate to high, depending on the isoform, affinity. The AMPA and NMDA receptors are also named for selective ligands that are synthetic analogues of aspartate and glutamate, respectively. Other receptors are named using some combination of the natural ligand and letters and numbers, as is the case for the 5HT₃, GABA_A, and P2X receptors.

receive prophylactic 5-HT₃ receptor antagonists to prevent the otherwise inevitable feeling of nausea and consequent vomiting. The ionotropic purinergic receptor family, P2X, mediates fast pain, as well as visceral signals such as bladder-filling.

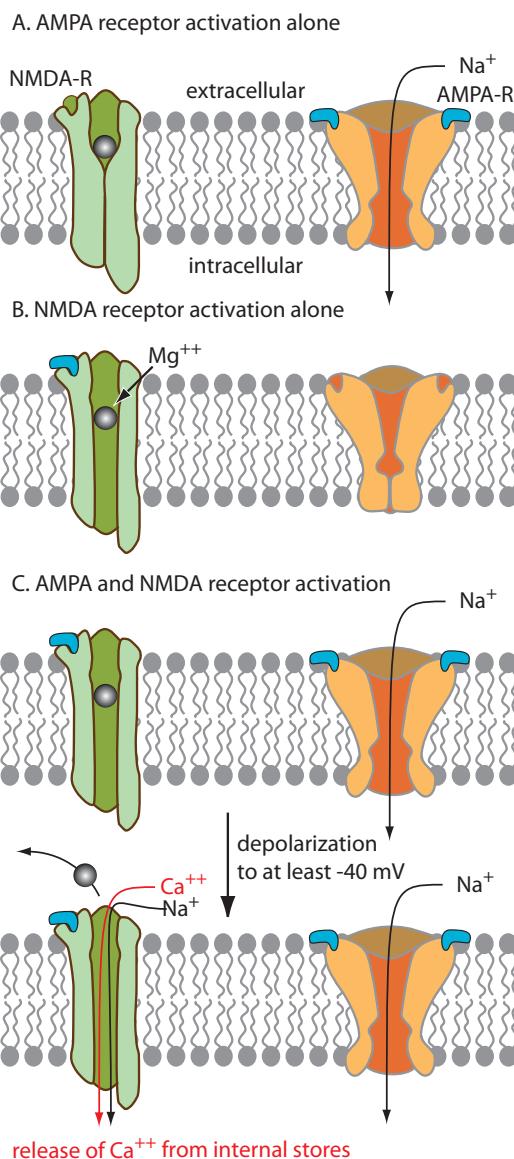
GLUTAMATE BINDS TO AND OPENS TWO FUNDAMENTALLY DIFFERENT IONOTROPIC RECEPTORS

When activated by glutamate, AMPA receptors mediate fast, excitatory transmission by forming a pore that conducts both sodium and potassium ions (see Fig. 4-6). The rapid depolarization due to flux through AMPA receptors constitutes the majority of the excitatory transmission in the CNS. The AMPA receptors not only open rapidly but also rapidly **desensitize**, meaning the receptor pore closes and is insensitive to ligand-gated opening for a period of time. Because of these two kinetic features, *AMPA receptor-mediated synaptic potentials are punctuated, starting and ending quickly, within milliseconds.*

Glutamate also binds to a second ionotropic receptor, the N-methyl-D-aspartic acid (**NMDA receptor**). Activation of the NMDA receptor involves a unique hitch not seen with other receptors. Normally, a magnesium ion, Mg⁺⁺, **blocks** the NMDA receptor pore from the extracellular side. The magnesium ion is secured in place by electrostatic attraction to the inside of the negatively charged neuron (Fig. 8-2A-B). When a neuron depolarizes, the positively charged magnesium ion is repelled by the positive potential of the neuron (Fig. 8-2C). The magnesium ion leaves the pore and reenters the extracellular milieu. Once the **magnesium block** is **relieved**, or removed, activation of the NMDA receptor by glutamate causes a depolarization.

As a result of the magnesium block, NMDA receptor activation alone does not result in a depolarization. This is because, in the absence of a coincident depolarization, the magnesium block occludes the NMDA receptor. Thus, even when the NMDA receptor binds glutamate and the NMDA pore opens, the pore is still blocked and no ion flux occurs (Fig. 8-2B). In contrast, when glutamate binds a NMDA receptor *at the same time* as a large depolarization occurs, typically through the activation of AMPA receptors, the magnesium block of the NMDA receptor will be relieved and current flow through the open pore (see Box 8-3) will occur (Fig. 8-2C). The current is comprised of sodium, potassium, *and* calcium ions. The influx of calcium ions through NMDA channels in turn triggers a massive release of calcium ions from internal stores. The resulting high concentration of free calcium ions acts as an important second-messenger to exert additional effects (see Box 8-4). The permeability of the NMDA channel to calcium ions and the release of calcium ions from intracellular stores are important because they

Figure 8-2. Glutamate (blue symbol as in Figure 4-6) elicits different effects, ranging from nothing to a large excitation, according to the receptors present on the postsynaptic membrane. A: When glutamate acts on AMPA receptors alone, a rapid and brief depolarization, carried by an influx of sodium ions and tempered by an efflux of potassium ions (not shown), results. B: When glutamate acts on N-methyl-D-aspartic acid (NMDA) receptors alone, there is no effect because the pore is blocked by external Mg⁺⁺. C: If glutamate, acting on AMPA receptors, produces a sufficient depolarization to dislodge the magnesium block of NMDA receptors, then the NMDA channel carries an inward current, which includes influx of both sodium and calcium ions. The calcium ion influx triggers release of more calcium ions from internal stores, which in turn perpetuates the relief of the magnesium block. Note that calcium ions act as second-messengers, and in this role, they elicit numerous physiological changes. Glutamate acting on AMPA receptors is the most common cause of a depolarization of sufficient magnitude to relieve the magnesium block of the NMDA receptor. Yet, any depolarization to at least -40 mV may relieve the magnesium block.



result in a high concentration of free calcium ions that, in turn, has two important effects:

- It causes further depolarization, which consequently produces prolonged relief from magnesium block.
- The calcium ions act as second-messengers, and as such, alter enzymatic activity to modify ion channel activity, cytoskeletal proteins, and gene expression.

The activation of NMDA receptors during the persistent relief from magnesium block produced by a depolarization allows additional NMDA receptor activation and more calcium ion entry, more release of calcium ions from internal stores, and so on.

Box 8-3

ANGEL DUST BLOCKS IONIC FLOW THROUGH THE NMDA RECEPTOR PORE.

Phencyclidine or **PCP**, colloquially referred to as **angel dust**, binds to a site located within the pore of the NMDA receptor and thus prevents current from flowing through the NMDA channel. Recall that the NMDA receptor is nearly ubiquitous within the brain, present on the majority of neurons including those of the cerebral cortex. From this vantage point, it is not surprising that PCP, and other drugs that antagonize NMDA receptor opening, such as **ketamine**,

or **Special K**, produce strong psychotropic effects. In normal adults, NMDA receptor antagonists that bind to the PCP-binding site produce a **dissociative** state that disconnects sensation from cognition, so that one feels separate from one's own body. PCP and ketamine also produce hallucinations and disordered thought that are thought to resemble, and therefore are used to model, the cognitive experience of patients suffering from **schizophrenia**.

The changes in cell physiology consequent to the relief of the NMDA block play a critical role in the **synaptic plasticity** that is thought to underlie learning and memory, as we explore in the next section.

GLUTAMATE'S ACTIONS AT NMDA RECEPTORS ARE CRITICAL TO LEARNING

Since the NMDA channel only opens if there is a simultaneous depolarization large enough to displace the magnesium ion block, the NMDA receptor forms a molecular **coincidence detector**. In other words, neither glutamate alone nor depolarization alone will open the NMDA receptor but glutamate plus depolarization will. Thus, if a cell becomes sufficiently depolarized, perhaps from the activation of

Box 8-4

ACTIVATED NMDA RECEPTORS ENGAGE CALCIUM IONS AS SECOND-MESSENGERS.

The NMDA receptor is an exception to the rule that ionotropic receptors act only through direct channel opening. When activated, the NMDA receptor forms a pore through which cations, including calcium ions entering the cell, flow. These calcium ions

interact with protein kinases, phosphatases, and other enzymes as second-messengers. Thus, the NMDA receptor not only opens a channel but also results in second-messenger, in this case calcium ions, recruitment.

AMPA receptors, the magnesium block will be relieved, permitting NMDA receptor activation by glutamate.

As noted above, the NMDA channel is permeable to calcium ions. Elevated intracellular levels of calcium ions resulting from NMDA channel opening lead to important changes that are collectively considered as the top candidate for the cellular mechanism of hippocampal learning. Most importantly, an elevated calcium ion concentration activates a number of protein kinases that phosphorylate both AMPA receptors existing within the plasma membrane and molecules involved in the trafficking, or movement, of cytoplasmic AMPA receptors that have been synthesized but not yet inserted into the membrane and are therefore not yet available or active. The net effect of the phosphorylation steps is that larger currents flow through existing AMPA receptors *and* that additional AMPA receptors are inserted into the plasma membrane. Because there are more AMPA receptors, and these AMPA receptors have been modified to carry greater currents, a glutamatergic input will evoke a substantially larger response than it did prior to these **plastic** changes. In other words, the response to an input has been modified or changed as a result of its association with another input.

The process of augmenting the response to one input after it has occurred while the postsynaptic cell is strongly depolarized, termed **long-term potentiation**, can lead to the association of one input with another. Such a learned association may underlie certain forms of memory formation (see Box 8-5). The particular details of learning described here derive from work in the hippocampus, the region of cerebral cortex where didactic memories are formed (see Chapter 13). In other regions of the brain, slightly or even radically different cellular mechanisms support the formation of other types of memories.

Box 8-5

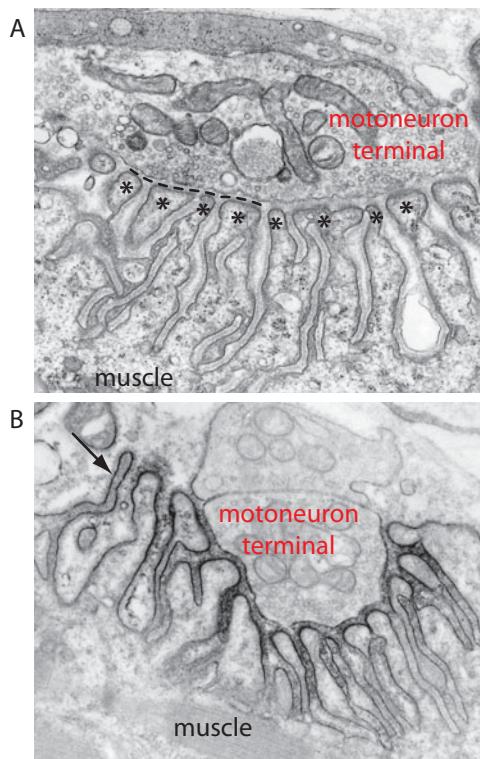
FORGETTING IS AS IMPORTANT AS MEMORY FORMATION IN NAVIGATING THE WORLD.

Effective learning requires a process to undo learning, a process referred to as *forgetting*, when conditions change. Indeed, in *The Mind of a Mnemonist*, Alexander Luria wrote of S, a man with a uniquely lopsided capacity to make memories but no ability to forget. S's striking ability came with its own disadvantages. As he locked all images and experiences into memory, S could not distinguish internal thoughts and images from external realities. A popular hypothesis holds that, in the hippocampus, the putative cellular process of learning, long-term potentiation, is opposed by a putative

cellular form of forgetting, **long-term depression**. When two inputs that had previously occurred together occur repeatedly at different times, the association is then weakened through long-term depression. The mechanisms of long-term depression in the hippocampus are the reciprocal of those involved in long-term potentiation. In hippocampal long-term depression, there is a reduced AMPA receptor-mediated current and internalization of AMPA receptors, leading to fewer and less effective receptors present in the postsynaptic membrane.

Figure 8-3. In a normal human neuromuscular junction or endplate, a motoneuron axon ends upon a skeletal muscle fiber. A: The muscle contains junctional folds (asterisks in A) across from the many active zones within the axonal terminal. A basal lamina (dashed line in A) runs between the axonal plasma membrane and the muscle. B: At the top of each junctional fold, acetylcholine receptors are concentrated (arrow in B) and at the base of the folds, voltage-gated sodium channels are concentrated (not shown). Acetylcholinesterase is anchored to the basal lamina.

Photomicrograph kindly provided by Andrew G. Engel of the Mayo Clinic.



NICOTINIC ACETYLCHOLINE RECEPTORS MEDIATE NEURONAL COMMUNICATION WITH SKELETAL MUSCLES AND THUS ARE CRITICAL TO LIFE

The most thoroughly understood synapse is the neuromuscular junction or **endplate**, where a motoneuron axon contacts a skeletal muscle fiber that expresses nAChRs (Fig. 8-3). An action potential in a motoneuron results in the release of thousands of acetylcholine molecules from each of hundreds of vesicles. Thus, it is estimated that an action potential in one motoneuron results in the release of *millions* of molecules of acetylcholine onto a single postsynaptic muscle fiber. Released acetylcholine diffuses across the synaptic cleft, itself densely packed with acetylcholinesterase, an enzyme that degrades acetylcholine (see Chapter 7), to reach the receptors. Although most of the acetylcholine molecules released are hydrolyzed by acetylcholinesterase, enough make it to the postsynaptic membrane to elicit a response in the muscle. This response is mediated by activation of nicotinic receptors, which are crowded at very high density, more than 10,000 receptors per square micron (see Box 8-6). The receptors are concentrated on the muscle membrane at a location exactly opposite to axonal release sites. As is the case for AMPA receptors, activated nicotinic receptors form an open channel through which sodium and potassium ions pass. The extracellular acetylcholinesterase present in the synaptic cleft ensures that the effect of acetylcholine released by a single action potential is short-lived.

Box 8-6

PATIENTS WITH MYASTHENIA GRAVIS HAVE A REDUCED NUMBER OF NICOTINIC ACETYLCHOLINE RECEPTORS AT THE NEUROMUSCULAR JUNCTION.

Patients with **myasthenia gravis** present with muscle weakness, often of the eyelids, resulting in ptosis. The most common form of myasthenia gravis results from the production of antibodies that compromise the clustering or integrity of acetylcholine receptors present at the endplate. The antigen targeted by antibodies in myasthenic patients varies with most antibodies directed against the nicotinic acetylcholine receptor. The pathological antibodies activate complement and thereby lead to the degradation of the postsynaptic membrane. A minority of patients have antibodies that recognize a muscle-specific kinase, **MuSK**, an enzyme critical to the clustering of nicotinic receptors at the end plate. Genetic forms

of myasthenia result from congenital mutations in a variety of proteins involved in endplate formation and function. Regardless of the particular pathophysiology involved, muscle contraction rapidly fatigues upon repeated stimulation in the myasthenic patient. This rapidly fatiguing weakness stands in marked contrast to the initial weakness that improves with continued use observed in patients with Lambert-Eaton syndrome (see Box 6-2). To increase the amount of acetylcholine available to bind to the diminished number of nicotinic receptors, patients with myasthenia gravis are treated with cholinesterase inhibitors (see Chapter 7).

Box 8-7

THE NEUROMUSCULAR JUNCTION IS A MORE RELIABLE SYNAPSE THAN MOST SYNAPSES IN THE BRAIN.

The safety factor is the ratio of the output to the input. A safety factor of unity would mean that every presynaptic action potential elicits a muscle action potential, and therefore a contraction, whereas a safety factor of 0.5, for example, would mean that half of the incoming potentials elicit muscle contraction. In healthy individuals, the safety factor of the neuromuscular junction is typically greater than 0.5. In contrast, many central synapses have a safety factor of considerably less than 0.5.

At an individual neuromuscular junction, a single action potential opens tens of thousands of channels and produces a depolarization in the target muscle fiber that typically reaches threshold for an action potential. Thus neuromuscular transmission enjoys a high **safety factor**, meaning that transmission from the motoneuron axon to muscle contraction succeeds more often than it fails (see Box 8-7). The high safety factor ensures that essential functions like breathing, moving about, and eating happen. It also follows that motor weakness at the neuromuscular junction is typically a sign that the synapse has been severely compromised.

In contrast to the neuromuscular junction, a typical hippocampal neuron (modern neurobiology's favorite model of a central neuron) integrates a large number of synaptic inputs from a variety of sources. At any single hippocampal glutamatergic synapse, a presynaptic action potential results in the release of only a single vesicle, on average, which in turn opens fewer than a hundred AMPA channels. As a result, the postsynaptic neuron may respond with an excitatory post-synaptic potential (EPSP), but is unlikely to fire an action potential due to a single glutamatergic input. Such central synapses, with a low safety factor, are ideal for situations that require the integration of a large number of synaptic inputs. In contrast, at the neuromuscular junction, there is only one input—from the motoneuron axon—and the safety factor is relatively high.

THE NICOTINIC RECEPTOR COMES IN A NUMBER OF VARIATIONS, EACH OF WHICH IS PRESENT IN DIFFERENT TISSUES

Nicotinic acetylcholine receptors, like all other ionotropic receptors, are **multimeric** complexes, meaning that several subunits assemble into one functional receptor complex. For each subunit, there may be numerous genes, as well as potential post-translational modifications. Therefore, there are a number of different subtypes of receptors depending on the particular subunit makeup. In the case of the nAChR, there are three primary subtypes:

- The muscle nicotinic receptor, present on all skeletal muscle, mediates the communication between a motoneuron axon and a skeletal muscle fiber (see Box 8-8).
- The ganglionic nicotinic receptor is present in all *autonomic* ganglia and mediates the communication between an autonomic motor neuron and a ganglionic neuron.

Box 8-8

ANTAGONISTS AT THE MUSCLE NICOTINIC RECEPTOR CAN BE LETHAL OR AT CERTAIN DOSES, CAN ACT AS A MUSCLE RELAXANT.

Curare, a plant alkaloid placed by South American natives on the tips of arrows, is a nicotinic receptor antagonist that blocks the muscle nicotinic receptor but not the ganglionic nicotinic receptor. The natives shot curare-tipped arrows into prey. The prey lost control of their muscles, fell out of trees, and were then killed by the natives. Even if the natives had not killed them, the prey would have died eventually as curare would paralyze the diaphragm, the muscle needed for inspiration. The natives could safely eat the prey as curare is too large and charged to be absorbed across the gastrointestinal lining.

Pancuronium, pharmacologically similar to curare, is one of the drugs contained in the lethal injection administered to prisoners executed in the United States. However, as pancuronium paralyzes without producing analgesia, at least two states,

Ohio and Washington, have recently dropped pancuronium from the lethal injection protocol. At low doses, pancuronium is also used as a muscle relaxant for surgery. Within the emergency room, **succinylcholine**, a short-acting nicotinic receptor agonist, is administered to relax the muscles of a patient to allow a health professional to **intubate**, or place a tube into the trachea of a patient, without the patient gagging. Succinylcholine depolarizes skeletal muscle, preventing the muscle from firing action potentials (see Chapter 5). Although it resists immediate degradation by acetylcholinesterase, succinylcholine is hydrolyzed by plasma esterases within about 10 minutes. Whenever using such a muscle relaxant, a means of artificially ventilating a patient must be available in case the need should arise.

- The neuronal nicotinic receptor is present in the brain and mediates communication between two central neurons.

Although nicotine activates all three subtypes (see Box 8-9), albeit only at high concentrations in the case of the muscle nicotinic receptor, distinct sets of receptor agonists and antagonists are effective in selectively blocking the muscle, ganglionic and neuronal receptors.

GABA BINDS TO AND OPENS THE IONOTROPIC GABA_A RECEPTOR

When GABA binds to a GABA_A receptor, the receptor changes conformation and forms a pore that is permeable to chloride ions. As detailed in Chapter 4, the reversal potential for chloride ions depends on the distribution of chloride ions, which in turn depends on the type of chloride transporters active in a cell. In most neurons in the adult nervous system, the KCC transporter, which you recall transports chloride ions out of the cell, dominates, so that the Nernst potential for chloride ions is about -70 mV. Since neurons typically have resting

Box 8-9

NICOTINE PRODUCES BOTH SYMPATHOEXCITATION AND PSYCHOTROPIC EFFECTS.

Nicotine, a selective agonist at the nicotinic acetylcholine receptor, is the major active ingredient in tobacco. As the reader is likely aware, nicotine is one of the most widely used drugs of the modern world. Nicotine has two major effects:

- Sympathetic stimulation
- Psychotropic effects including alertness, relaxation, reduced appetite, and enhanced focus of attention

Nicotine has little to no effect on skeletal muscle as it is a poor agonist at the muscle nicotinic receptor.

Nicotine's sympathoexcitatory actions include elevations in cardiac output, blood pressure, and heart rate and also epinephrine release from the

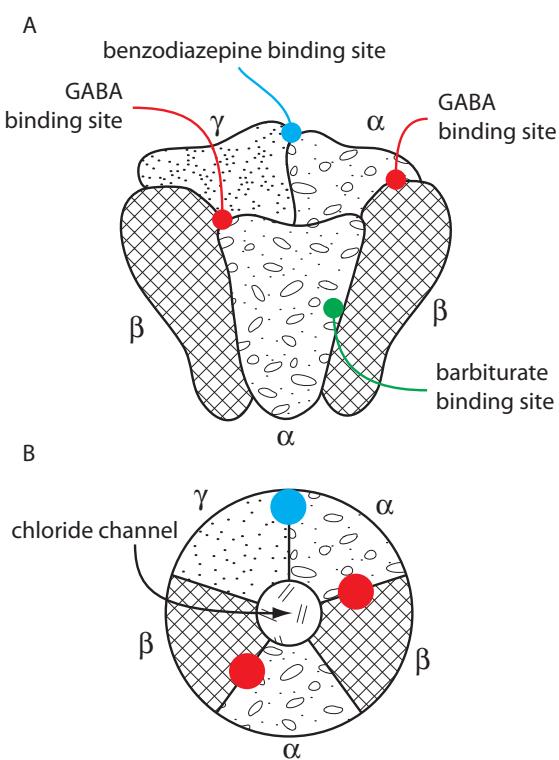
adrenal medulla. The stimulatory effects of epinephrine contribute to nicotine's psychotropic effects. Many individuals who use tobacco develop a strong dependence or addiction to nicotine. Dependence on nicotine, a common and costly problem today, stems from nicotine's actions in the central nervous system. By replacing an addiction to cigarettes with a dependence on nicotine patches or gum, smoking cessation programs parse the addiction, separating a patient's dependence on the act of smoking and the full complement of tobacco ingredients from the dependence on nicotine per se. Patients who successfully quit smoking but continue to take in nicotine reduce their risk of lung disease but may still suffer from other negative consequences of the drug, most notably adverse cardiovascular effects.

potentials of about -50 to -60 mV, activation of the GABA_A receptor usually causes chloride influx and a hyperpolarization, and thus inhibits, most neurons.

As the predominant fast inhibitory receptor in the CNS, the GABA_A receptor is central to the actions of many therapeutics including general anesthetics, anxiolytics, hypnotics and anticonvulsants as well as alcohol. Benzodiazepines, a large class of drugs that includes anxiolytics, muscle relaxants and hypnotics, bind to a site on the GABA_A receptor distinct from the site where GABA binds (Fig. 8-4). A third site on the GABA_A receptor binds barbiturates, including a number that are effective as anticonvulsants. The affinity of a GABA_A receptor for GABA increases when the receptor is also bound to a benzodiazepine and/or to a barbiturate. Alcohol and general anesthetics beyond barbiturates facilitate and may even act as an agonist at the GABA_A receptor. Ultimately, benzodiazepines, barbiturates, alcohol, and general anesthetics result in more chloride ion influx. Because of the ubiquity of GABA_A receptor distribution, these drugs cause a widespread inhibition of brain function that produces behavioral consequences such as sedation.

Like the nAChR to which it is closely related, the GABA_A receptor is made up of multiple subunits. A highly diverse set of subunit isoforms results in a large number of possible subunit combinations. Different drugs bind to different subunit combinations that are expressed in different neurons so that, for example, one drug has the predominant effect of inhibiting anxiety while a different drug primarily inhibits movement.

Figure 8-4. Five subunits—two α subunits, two β subunits, and one γ subunit, make up the GABA_A receptor. Two γ -aminobutyric acid (GABA) binding sites are present at the α - β interfaces, and both have to be occupied for the pore, a chloride channel, to open. A site that binds benzodiazepines and a limited number of related compounds is located at the α - γ interface. General anesthetics act at a few sites within the lipid bilayer. For example, barbiturates that have both anticonvulsant and general anesthetic action, bind at the α - β subunit interface within the lipid bilayer. Other general anesthetics act elsewhere within intramembranous regions of the GABA_A receptor. Panel A shows an oblique side view of the receptor and B a top-down view of the receptor.



METABOTROPIC RECEPTORS ACT INDIRECTLY TO OPEN, CLOSE, OR OTHERWISE MODIFY ION CHANNELS

The vast majority of receptor types are metabotropic and act through membrane-associated G proteins. Although the effects of metabotropic receptor activation vary, the following fundamental properties are nearly universal across all metabotropic effects:

- *Slow onset:* Metabotropic receptor activation acts indirectly on ion channels. Thus, the onset of resulting changes in conductance is never as fast as changes elicited by ionotropic receptor activation.
- *Modification of ion channels:* Metabotropic receptor activation can lead to the opening, closing, or to the modification of an electrical property, such as the desensitization rate, of ion channels. In contrast, ionotropic receptor activation always leads to channel-opening.
- *Nonelectrical effects:* Metabotropic receptor activation can lead to changes in cell physiology, changes in the expression and trafficking of proteins, the shape of a cell, or a number of other nonelectrical properties of a cell.
- *Dependence on intracellular signaling molecules:* Activation of the same metabotropic receptor may have different, even opposing, effects in different cells. For example, the same metabotropic receptor, acting via the same G protein isoform, can act on different *adenylyl cyclase* isoforms to produce different effects.

In this chapter, we focus on common mechanisms by which metabotropic receptor activation results in ion channel modification. Additionally, we review commonly used clinical drugs that either mimic or antagonize metabotropic receptor-mediated signaling.

ACTIVATION OF METABOTROPIC RECEPTORS ACTIVATES G PROTEINS, WHICH IN TURN ACTIVATE A VARIETY OF EFFECTORS

Dozens of different isoforms of the three required subunits— α , β , and γ —make up the G proteins linked to metabotropic receptors. G proteins that bind to metabotropic receptors are associated with the inner leaflet of the cell membrane. At rest, all three subunits are bound together with a

guanine diphosphate (GDP) molecule bound to the α subunit (Fig. 8-5). Upon stimulation by an activated receptor, guanine triphosphate (GTP) is exchanged for GDP and the α subunit dissociates from the β - γ subunits. The β and γ subunits never dissociate under physiological conditions. After activation, both the α subunit bound to GTP, free to diffuse through the cell, and the β - γ subunits, largely restricted to the inner leaflet of the cell membrane, can directly affect channels or enzymes.

G protein activation is terminated when the α subunit itself hydrolyzes GTP to form GDP, allowing the α subunit to reassociate with the β - γ subunits (Fig. 8-5). Yet, the reassociated G protein can become activated again by binding to a metabotropic receptor, which is itself bound to an agonist. Thus, *for as long as a G protein-coupled receptor remains bound to an agonist, it can continue to activate G proteins*. This cycle greatly *amplifies* the effect of ligand binding to a metabotropic receptor, allowing many iterations of G protein activation per ligand binding event. In addition, each activated G protein can trigger the production of many molecules of a second-messenger, which can, in turn, lead to the production of additional second-messenger species or varieties. In this way, the binding of an agonist to a G protein-coupled receptor can set into motion a **second-messenger cascade**, in which increasing numbers of second-messenger species and increasing numbers of molecules of each species are produced through successive waves of biochemical activity, thereby greatly amplifying the effect of activation of a single receptor.

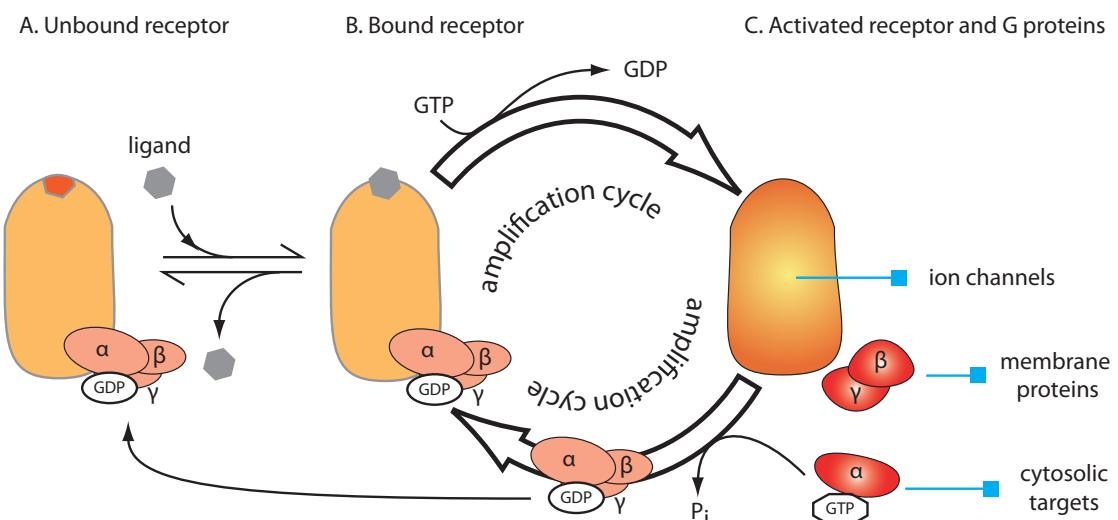


Figure 8-5. Metabotropic receptor activation lasts as long as a ligand is bound to the receptor. **A:** At rest, a metabotropic receptor is bound to a G protein, which is bound to guanine diphosphate (GDP). Three subunits— α , β , and γ —make up a G protein. The α subunit binds GDP in the resting state. When a ligand binds to a metabotropic receptor (**B**), the GDP that is bound to the α subunit is exchanged for a guanosine triphosphate (GTP; **C**), and the receptor and associated G protein are activated. The activated receptor can affect ion channels within the membrane. The β and γ subunits stay bound together, and when activated, can affect membrane-associated proteins. The activated α subunit, bound to a GTP molecule, diffuses throughout the cell and can affect a large variety of cytosolic targets, as well as distant membrane protein targets. When the α subunit hydrolyzes GTP into GDP, releasing a phosphate ion (P_i) in the process, it rapidly reassociates with the β - γ subunits. The G protein can then associate with either a receptor bound to a ligand or to an unbound receptor. If the G protein associates with a ligand-bound receptor, another round of activation of the receptor, β - γ subunits, and α subunit occurs.

Many metabotropic receptors act indirectly through second-messengers, most of which are engaged by the activated, GTP-bound, α subunit. The most prevalent second-messengers are:

- **Adenyl cyclase** activation leads to cyclic adenosine monophosphate (**cAMP**) production, which in turn activates a number of **cAMP-dependent protein kinases**. In a parallel pathway, **guanylyl cyclase** activation leads to cyclic guanosine monophosphate (**cGMP**) production. Unlike cAMP, cGMP exerts its predominant effect by opening or closing **cyclic nucleotide gated channels**.
- **Phospholipase C** activation leads to production of **diacylglycerol (DAG)** and **inositol trisphosphate (IP₃)**, which in turn lead to activation of **protein kinase C (PKC)** and the release of calcium ions from internal stores, respectively.
- **Phospholipase A₂** activation leads to production of **arachidonic acid**, which in turn leads to production of a variety of further signaling molecules, such as **prostaglandins, prostacyclins, and leukotrienes**.

Second-messengers that derive from the membrane—DAG and arachidonic acid—primarily stay associated with the plasma membrane, whereas soluble second-messengers such as calcium ions, cyclic nucleotides, and IP₃ exert effects throughout the cytosol, as well as on membrane proteins.

THE VARIETIES OF G PROTEINS, SECOND-MESSENGERS, AND EFFECTOR PATHWAYS PROVIDE GREAT FLEXIBILITY TO THE POTENTIAL EFFECTS OF METABOTROPIC RECEPTORS

Due to the great variety of metabotropic receptors, second-messengers, and potential effectors, a single neurotransmitter can have many different effects, including excitatory, inhibitory, and electrically silent ones. *G proteins with different α subunits can have opposing effects on the same second-messenger system.* For example, G proteins containing **Gas** (the s is for stimulatory) stimulate cAMP production, whereas G proteins containing **Gai** (the i is for inhibitory) inhibit cAMP production (see Box 8-10). In this way, a neurotransmitter that binds to a metabotropic receptor can either open or close an ion channel through an effect on the same second-messenger. A classic example of this involves the autonomic control of heart rate. Parasympathetic and sympathetic neurons influence heart rate through effects on cells in the **sinoatrial node** within the right atrium that pace cardiac contractions. Acetylcholine, released from parasympathetic nerves, binds to a **muscarinic receptor**, a metabotropic receptor named after **muscarine**, a plant compound that selectively activates these receptors (see Box 8-2). The activated muscarinic receptor activates a G α i-containing G protein, resulting in a reduction in cAMP production.

G PROTEINS ARE TARGETED BY PERTUSSIS AND CHOLERA TOXINS.

Two toxins—**pertussis** and **cholera**—wreak physiological havoc, and in the case of cholera toxin, cause death if left untreated. Pertussis toxin causes **whooping cough** primarily through effects on the respiratory epithelium. Cholera toxin causes cholera, still a major threat in developing countries primarily in sub-Saharan Africa, by initially attacking the gastrointestinal epithelium. Pertussis toxin binds to and interferes with the function of certain isoforms of G α i, inhibitory G protein subunits, whereas cholera toxin blocks the function of certain isoforms of G α s,

stimulatory G protein subunits. Both toxins cause exclusively or predominantly non-neurological symptoms in large part because their access to the nervous system is restricted, or at least delayed, by the blood–brain barrier. The whooping cough caused by pertussis toxin and severe diarrhea caused by cholera toxin reflect the access of toxin to vulnerable barrier tissues, as well as the ubiquity of G protein signaling in physiological function, neural and non-neuronal alike.

The reduction in cAMP levels decreases the activity of cAMP-dependent **protein kinase A** (PKA), and in turn the phosphorylation state of calcium channels. A decrease in phosphorylation renders calcium channels less likely to open at rest potentials. Along with an increase in potassium channel activity produced by the activated β - γ subunits of the G protein, the decrease in calcium channel activity hyperpolarizes cardiac pacemaker cells, prolonging the interval between action potentials and therefore between heart beats. In contrast, norepinephrine, released from sympathetic nerves, acts at **adrenergic receptors** to activate a G α s-containing G protein that increases cAMP production and PKA activity, thereby increasing the phosphorylation state and consequently the activity of calcium channels. Thus, *a neurotransmitter bound to a metabotropic receptor can lead to the opening, closing, or modulation of a channel, whereas a neurotransmitter bound to an ionotropic receptor can only lead to the opening of a channel.*

Another avenue of cyclic nucleotide signaling is exemplified by the process of **phototransduction**, changing light energy into electrical energy, in the retina. In the absence of light stimulation, photoreceptors, a special class of retinal cells that respond to light, have a relatively high concentration of cGMP, which directly binds to and opens cyclic nucleotide gated cation channels (see Box 8-11). In the dark, cGMP levels are high, and cyclic nucleotide gated channels are open. This means that in the dark, photoreceptors have an inward cation current, carried by sodium and calcium ions, that depolarizes them to about -40 mV (Fig. 8-6A). Light stimulation activates **transducin**, a particular type of G protein, contained within photoreceptors, that is activated by photons. When activated, the α subunit of transducin, bound to GTP, activates **phosphodiesterase**, which then degrades cGMP. The result of phosphodiesterase activity is a lowered concentration of cGMP and therefore less inward cation current, resulting in a hyperpolarization (Fig. 8-6B). And, yes, this physiological trick is unusual: Photoreceptors are the only sensory cells that are hyperpolarized by stimulation.

THE CYCLIC GUANOSINE MONOPHOSPHATE (cGMP)-GATED SODIUM CHANNEL IN PHOTORECEPTORS IS ESSENTIAL TO PHOTORECEPTOR HEALTH.

Mutations in the cyclic nucleotide-gated channel present in retinal photoreceptors can impair vision. Some of these mutations lead to a form of **retinitis pigmentosa**, a disease in which the photoreceptors degenerate. Although it is straightforward to understand how mutations in the photoreceptor cyclic nucleotide-gated channel would impair phototransduction, it remains unclear why photoreceptors with mutated channels eventually die as a result of this

deficit. Other mutations in the photoreceptor cyclic nucleotide-gated channel lead to a form of congenital **achromatopsia**. In this disease, the three types of photoreceptor responsible for seeing both color and high-acuity forms lack functional cyclic nucleotide-gated channels and therefore do not function at all. Patients with achromatopsia can see light and dark and general forms but cannot see colors or detailed forms (for more information see Chapter 16).

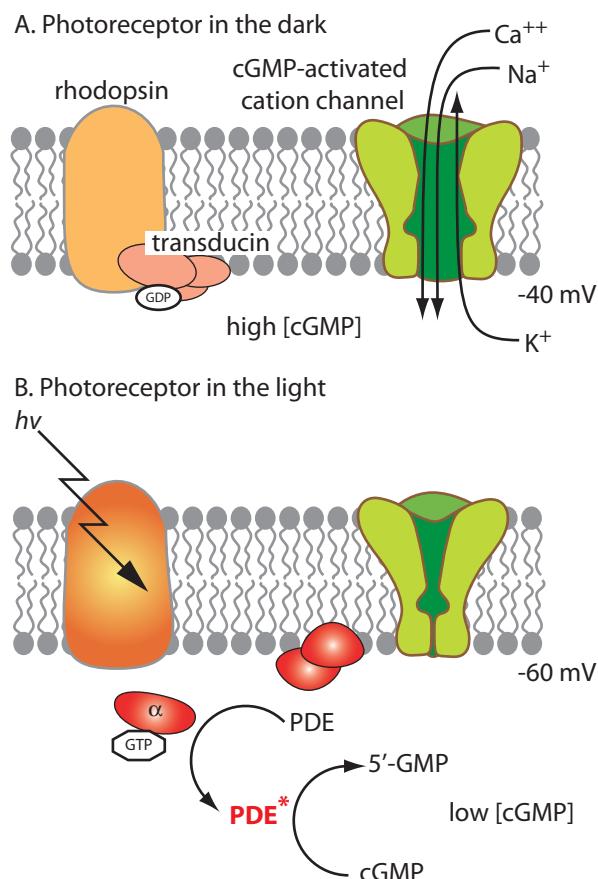


Figure 8-6. A: Photoreceptors have a “dark current,” an inward current that persists in the absence of light. Cyclic nucleotide gated cation channels, activated by a high resting concentration of cyclic guanosine monophosphate (cGMP) carry the dark current. B: Light ($h\nu$) activates rhodopsin, which activates a G protein called transducin. The activated α subunit of transducin activates cGMP phosphodiesterase, which converts cGMP into 5'-GMP, thus lowering the concentration of cGMP in the photoreceptor. As a result of the decrease in cGMP concentration, cyclic nucleotide-gated cation channels close and the cell hyperpolarizes.

Box 8-12

INHIBITION OF CYCLIC GUANOSINE MONOPHOSPHATE (cGMP)-ACTIVATED PHOSPHODIESTERASE PROLONGS ERECTIONS AND MIMICS THE EFFECT OF LIGHT ON PHOTORECEPTORS.

Sildenafil, commonly known as **Viagra**, is an inhibitor of the cGMP-activated phosphodiesterase. Sildenafil is approved to treat **erectile dysfunction** in America. By inhibiting the cGMP-selective phosphodiesterase that is present in the penis' corpus cavernosum, sildenafil prolongs the vasodilation produced by cGMP production. As it turns out, the phosphodiesterase present in the penis is the same type present in retinal photoreceptors. When sildenafil prolongs the activation of photoreceptors, the result is “seeing blue,” a symptom termed **cyanopsia**.

Box 8-13

S-NITROSYLATION REFERS TO THE ADDITION OF NITRIC OXIDE (NO) TO A CYSTEINE.

S-nitrosylation refers to the addition of a nitric oxide to the sulfur in a cysteine, producing a **S-nitrosothiol**, R-S-N = O, where R is the rest of the protein, and S, N, and O refer to sulfur, nitrogen, and oxygen, respectively.

Like cGMP, cAMP also directly opens a number of cyclic nucleotide-gated channels, providing another avenue for cAMP signaling in addition to kinase activation. Furthermore, cAMP can act through a number of pathways beyond PKA and opening cyclic nucleotide gated channels. For example, cAMP can activate **guanine nucleotide exchange factors**, which in turn regulate the activity of **small GTPases**, soluble proteins such as **ras** that are small versions of the α subunit of membrane-bound G proteins and are present in the cytosol. The effects of such signaling are wide-ranging and include diverse, electrically silent modifications of cellular physiology.

Just as cAMP acts through a number of signaling pathways, cGMP can act through pathways beyond those involving phosphodiesterase described above. For example nitric oxide (NO), the gaseous neurotransmitter introduced in Chapter 7, results in the activation of soluble guanylyl cyclase and consequently the production of cGMP from GTP. In the periphery, cGMP production activates protein kinase G, which phosphorylates proteins that change the contractile properties of smooth muscle and results ultimately in relaxation (see Box 8-12). Within the CNS, NO acts both by increasing cGMP levels and by initiating the **S-nitrosylation** of a number of cytosolic proteins including ion channels, transporters, cytoskeletal components, and enzymes (see Box 8-13). Thus, NO acts as a signaling molecule and engages the production of additional signaling molecules such as cGMP.

METABOTROPIC RECEPTORS ACTIVATED BY NOREPINEPHRINE AND ACETYLCHOLINE ARE KEY TO CLINICAL PHARMACOLOGY THROUGH PERIPHERAL EFFECTS ON AUTONOMIC TARGETS

Dramatic clinical effects result from drugs that act at metabotropic receptors present in both pre- and postsynaptic elements of the synapse from autonomic ganglionic neurons onto their targets. Parasympathetic and sympathetic ganglionic neurons release either acetylcholine or norepinephrine, both of which act on target cells exclusively through the activation of metabotropic receptors. Acetylcholine acts at muscarinic receptors, which come in five major subtypes termed M_1 through M_5 . Norepinephrine acts at adrenergic receptors, which come in two basic varieties: α and β . Since autonomic targets are always peripheral, there is no requirement that a drug cross the blood–brain barrier, and indeed, drugs such as muscarine do not enter the CNS.

When the endogenous agonists, acetylcholine and norepinephrine, are released from autonomic neurons, they bind to a panoply of muscarinic and adrenergic receptors present on non-neuronal target tissues (see Box 8-14). By targeting cardiac muscle, glands, and smooth muscle tissues, autonomic neurons influence physiological function throughout the body. In many cases, this influence may operate simply by increasing or decreasing the blood flow to a

Box 8-14

SIGNALING FROM AUTONOMIC GANGLION NEURONS TO TARGET CELLS IS PREDOMINANTLY MEDIATED BY METABOTROBIC RECEPTORS.

Vesicles containing norepinephrine or acetylcholine, like virtually all synaptic vesicles, contain adenosine triphosphate (ATP). The ATP in autonomic ganglion axon terminals has important effects because autonomic target cells express purinergic receptors. Thus, ganglionic neurons communicate with target cells through purinergic, as well as muscarinic and adrenergic receptors. ATP binds to *ionotropic* P₂X receptors and metabotropic P₂Y receptors,

both of which are widespread throughout the body. Sympathetic neurons release an additional co-transmitter beyond norepinephrine and ATP: **neuropeptide Y**, or **NPY**. As is the case with all known neuropeptide receptors, NPY receptors are metabotropic. Therefore, autonomic signaling from ganglionic neurons is predominantly, but not exclusively (remember the P₂X receptors), mediated by metabotropic receptors.

Box 8-15

β-BLOCKERS DECREASE CARDIAC OUTPUT THROUGH EFFECTS ON CONTRACTILE FORCE AND RATE.

β-Blockers exert two effects on cardiac muscle:

- The **inotropic** (not in any way related to *ionotropic*) effect is to decrease the *force* of cardiac muscle contraction.
- The **chronotropic** effect is to decrease heart *rate*.

In addition, some β-blockers also decrease peripheral blood vessel resistance, an effect that decreases blood pressure (see Table 8-1). All three of the potentially desirable effects of β-blockers act to lower blood pressure. Therefore, β-blockers are often used to treat **hypertension**, or elevated blood pressure.

tissue through an effect on the smooth muscle supplying blood vessel walls. Thus, *drugs that either mimic or antagonize the synapse from autonomic ganglionic neurons to target tissues can influence the function of virtually every tissue in the body.*

Drugs that mimic the actions of acetylcholine are termed **parasympathomimetics**, and those that block the actions of acetylcholine are termed **parasympatholytics**. Under a similar nomenclature, drugs that mimic the actions of norepinephrine are termed **sympathomimetics**, whereas those that block the actions of norepinephrine are termed **sympatholytics**. These compounds comprise an important part of the pharmaceutical arsenal used by cardiologists, ophthalmologists, diabetologists, pulmonologists, urologists, and virtually every other clinical specialist, as well as by general practitioners. Additionally, because of the widespread expression of muscarinic and adrenergic receptors, most of the drugs that modify autonomic transmission have multiple physiological effects. In some instances, this may be clinically desirable, as is the case for β-blockers, β adrenergic receptor antagonists that decrease both heart rate and cardiac contractility (see Box 8-15). In other instances, the unwanted effects are undesirable, and thus colloquially termed “side effects.” As an example of the latter, a **decongestant** such as **phenylephrine**, an α adrenergic receptor agonist, constricts blood vessels in the nose and reduces nasal secretions, but also constricts blood vessels elsewhere and thus can cause hypertension at high enough doses. Table 8-1 lists a selection of commonly prescribed drugs that act on metabotropic muscarinic and adrenergic receptors in the periphery.

Although sympathetic and parasympathetic outputs occur outside of voluntary control, mood and affect can bias the autonomic nervous system toward either increased sympathetic or parasympathetic tone. For example, although we are unable to activate our lacrimal glands or increase cardiac contractility

TABLE 8-1. CLINICALLY USEFUL COMPOUNDS THAT ACT AS AGONISTS OR ANTAGONISTS AT SYNAPSES BETWEEN AUTONOMIC GANGLIONIC NEURONS AND PERIPHERAL TARGETS ARE LISTED

DRUG	RECEPTOR SUBTYPE	DRUG ACTION	USED TO TREAT
MUSCARINIC AGONISTS			
Pilocarpine	M ₃	Contracts ciliary muscle, which allows more aqueous humour drainage, thereby decreasing intraocular pressure	Glaucoma
Bethanechol	M ₃	Stimulates contraction of detrusor muscle; Stimulates gastrointestinal motility	Urinary retention, as an adjunct to an α-adrenergic antagonist (see below); Constipation
MUSCARINIC ANTAGONISTS			
Atropine	M ₁ – M ₅	Blocks vagal slowing of heart rate; Inhibits bronchoconstriction and mucus secretion from bronchi; Occupies muscarinic receptor binding sites	Cardiac arrest: Used as an adjunct to general anesthesia to prevent pulmonary edema; Prophylactic treatment for potential nerve gas exposure
Dicyclomine	M ₁ – M ₅	Inhibits peristalsis in the intestines and colon	Irritable bowel syndrome
Ipratropium, tiotropium, oxitropium	M ₁ – M ₅ , with some selectivity for M ₁ and M ₃	Blocks vagally mediated bronchoconstriction and mucus secretion, is not absorbed systemically when inhaled	Obstructive pulmonary disease such as emphysema and chronic bronchitis
Pirenzepine	M ₁	Inhibits vagally mediated gastric secretions	Gastric ulcers
Scopolamine	M ₁ – M ₅	Inhibits stimulation of central neurons that trigger vomiting	Motion sickness
Toleridone; oxybutynin	M ₁ – M ₅ M ₁ – M ₃	Inhibits parasympathetic activation of the detrusor muscle	Urinary incontinence
ADRENERGIC AGONISTS			
Epinephrine	All α and β	Causes vasoconstriction and increases blood vessel resistance, thereby reducing edema, via activation of α ₁ adrenergic receptors; increases bronchial dilation and cardiac output while decreasing the release of histamine and other mediators from mast cells via activation of β ₂ adrenergic receptors; Increases cardiac output and heart rate via activation of β ₂ adrenergic receptors	Anaphylactic reaction; Cardiac arrest
Oxymetazoline, xylometazoline, phenylephrine	α ₁	Stimulates vasoconstriction of blood vessels, so that when applied as a nasal spray, nasal secretions are inhibited	Nasal congestion

(Continued)

TABLE 8-1. CONTINUED

DRUG	RECEPTOR SUBTYPE	DRUG ACTION	USED TO TREAT
Apraclonidine, brimonidine	α_2	Inhibits secretion of aqueous humour from the ciliary body and facilitates drainage of same, thereby decreasing pressure in the eye	Glaucoma
Clonidine	α_2	Acts presynaptically to inhibit norepinephrine release from medullary sympathoexcitatory neurons, which in turn leads to a decrease in blood pressure due to reduced cardiac output and to vasoconstriction	Hypertension, particularly in patients undergoing withdrawal from narcotic use
Albuterol; formoterol; terbutaline; salmeterol	β_2	Increases bronchial dilation	Asthma

ADRENERGIC ANTAGONISTS

Alfuzosin, doxazosin, terazosin, tamsulosin	α_1	Relaxes the smooth muscle of the prostate as well as of the detrusor	Benign prostatic hypertrophy
Phenoxybenzamine	α_1	Binds to α_1 receptors on blood vessels, thereby blocking norepinephrine and epinephrine from binding and causing vasoconstriction	Hypertension in patients with pheochromocytoma, a malignancy of the adrenal medulla, which results in high levels of released epinephrine
Atenolol, acebutolol, bisoprolol, metoprolol, and many more	β_1	Slows heart rate and decreases cardiac output	Hypertension
Atenolol, esmolol, metoprolol	β_1	Slows heart rate and decreases cardiac output	Arrhythmias such as atrial fibrillation
Betaxolol	β_1	Inhibits secretion of aqueous humour from the ciliary body	Glaucoma
Nadolol, propanolol	$\beta_1 - \beta_2$	Slows heart rate, decreases cardiac output and blocks vasoconstriction	Hypertension
Timolol, levobunolol	$\beta_1 - \beta_2$	Inhibits secretion of aqueous humour from the ciliary body	Glaucoma

voluntarily, we can place ourselves into a sad or an agitated state, accompanied by tears or **tachycardia**, an elevation in heart rate, respectively. This type of affective influence over autonomic function lies at the heart of both **method acting** and **biofeedback**.

DRUGS ACTING ON ADRENERGIC RECEPTORS HAVE MIXED PERIPHERAL AND CENTRAL EFFECTS

In the heart, parasympathetic and sympathetic influences act in opposition to produce either a reduction or an increase in heart rate (see above). Yet, parasympathetic and sympathetic drugs do not always act in opposition. For example,

glaucoma can be treated by a muscarinic agonist, a parasympathomimetic, as well as by an α adrenergic agonist, expected to act as a sympathomimetic, or a β adrenergic antagonist, a sympatholytic. Glaucoma typically involves an increase in intraocular pressure, due to an increase in the pressure of the **aqueous humor**—containing **anterior chamber** of the eye (Fig. 8-7); even in cases when no increase in pressure occurs, decreasing intraocular pressure is beneficial. Therefore, therapy is aimed at decreasing the production of aqueous humor and/or increasing the drainage of aqueous humor. So, how can three different drugs have the same effect? We consider each class in turn.

- When administered in eye drops, pilocarpine, an agonist at the M_3 receptor, acts as acetylcholine does upon the **ciliary muscle**, leading to the muscle's contraction and an increase in the **iridocorneal angle** (Fig. 8-7). This in turn opens up the **trabecular meshwork** and increases outflow of aqueous humor, thereby decreasing pressure.
- α -2 Adrenergic agonists such as apraclonidine, activate α -2 adrenergic receptors on the ciliary body that activate $G\alpha_i$ that decreases cAMP production. As a result, the ciliary body produces less aqueous humor.
- β -Blockers such as timolol prevent endogenous norepinephrine from binding to β adrenergic receptors on the ciliary body. Since activating these receptors activates a $G\alpha_s$ protein that increases cAMP production, blocking the β receptor results in less cAMP production and consequently less production of aqueous humor by the ciliary body.

Since the drugs listed in Table 8-1 affect a large number of peripheral synapses, they often elicit side effects. These side effects can sometimes be circumvented by lowering the dose, targeting the route of administration and in a few cases, by tailoring the drug to an isoform found in a restricted set of tissues.

Many muscarinic drugs do not cross the blood–brain barrier, but even those that do, such as atropine, act entirely or primarily peripherally to produce therapeutic effects. Muscarinic antagonists used to counteract motion sickness, such as scopolamine, are exceptions to this rule as their site of action appears to be central, on chemoreceptive neurons of the medulla.

In contrast to the majority of muscarinic drugs, most commonly used adrenergic drugs act both peripherally and centrally. To understand how the central and peripheral consequences of adrenergic drugs interact, consider the conundrum addressed by William James: *are we afraid because we are running from the bear, or*

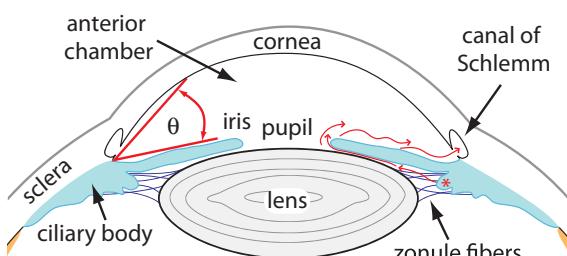


Figure 8-7. The ciliary body consists of ciliary muscles, which control pupillary size and lens shape, and the ciliary processes, which make aqueous humor. Aqueous humor is necessary to maintain the health of the lens and the anterior part of the eye, including the cornea and iris. Aqueous humor flows out from the ciliary processes through the zonule fibers. Aqueous humor flow follows a path between the iris and the lens, and then through the pupil to enter the anterior chamber. Aqueous humor bathes anterior tissues and flows through the trabecular meshwork, a spongy tissue that sits atop the iris, to exit the eye through the canal of Schlemm. The angle between the iris and the cornea, the iridocorneal angle, is larger in open-angle than in closed-angle glaucoma. Strategies at combating glaucoma are aimed at decreasing aqueous humor production or at increasing the iridocorneal angle to allow for greater aqueous humor drainage through the canal of Schlemm.

β -BLOCKERS MAY BLOCK RECONSOLIDATION OF TRAUMATIC MEMORIES.

Panic attacks are nature's version of "we are afraid because we are running from the bear." Massive sympathetic activation, marked by sweating, heart palpitations, rapid heart rate, dizziness, and even chest pain, occurs during a panic attack. As a result, the patient feels emotions of fear, loss of control, and panic. Patients with **post-traumatic stress disorder**, or PTSD, often react to stimuli reminiscent of a previous trauma with an emotional reaction and a generalized increase in sympathetic tone. To reduce the impact of such triggering events in PTSD, some therapists have paired recall of the traumatic event or exposure to triggers with administration of β -blockers. This allows reconsolidation of the traumatic memory without the ability to mount a generalized sympathetic reaction. The hope is that by repeatedly re-remembering a traumatic event while in a less sympathetically aroused state, individuals will become less anxious and upset when they recall that same event on their own.

do we run from the bear because we are afraid? In other words, to what extent does the sense of the body generate emotion, and to what extent does emotion drive the physical accompaniments to emotion? Although no definitive answer exists for this simple, yet profound, question, most agree today that the brain and body interact to produce emotion. For example, a person with a "pounding heart," reflective of elevations in heart rate and blood pressure, will have a difficult time maintaining a calm demeanor and impassive facial expression. Similarly, a person with a low heart rate and low blood pressure is unlikely to rage out of control. Under normal circumstances, an anxious body and an anxious mind occur together, as do a calm mind and body and so on. As an example of the interaction between body and brain, people are far less likely to remember emotional pictures if they originally viewed the pictures while taking a β -blocker, which prevents increases in heart rate and blood pressure (see Box 8-16). This experimental result shows that when the body mounts a sympathetic reaction to an event, stronger memories of the event result. Reinforced learning of events that elicit emotional reactions is likely the reason that we remember deeply moving events far more readily than we do mundane and banal occurrences.

GAP JUNCTIONS PROVIDE A DIRECT ROUTE OF INTERCELLULAR COMMUNICATION BETWEEN TWO CELLS

Gap junctions enable communication utilizing both electrical and second-messenger systems. These junctions are present throughout the body, including in nervous tissue, both peripheral and central. Within the nervous system, gap junctions are the physical substrate for **electrical synapses**, which differ from chemical synapses in several important ways:

- Both depolarizing and hyperpolarizing potentials are conveyed across an electrical synapse.
- There is no appreciable delay.
- Current carried by ions travels bidirectionally across many electrical synapses.
- The gap junction is a physical connection that allows molecules up to about 1 kilodalton to flow through. Thus, not only calcium and potassium ions but also small metabolites such as adenosine triphosphate (ATP) and adenosine diphosphate (ADP), and second-messengers such as IP_3 and cAMP flow through the gap junctions.

The gap junction is made up of two aligned **hemichannels** or half-channels, also termed **connexons**. Each hemichannel, made up of protein subunits called **connexins**, sits within the membrane of one cell. The gap between two cell membranes narrows to only 3 nm at the site of gap junctions, about 10-fold closer

Box 8-17

GAP JUNCTIONS PROVIDE OPEN CONDUITS BETWEEN NEURONS.

By providing an open, albeit small, conduit between cells, gap junctions support the idea of a many-celled syncytium. The structural continuity of two neurons connected by a gap junction compromises the physical discreteness of cells and thus is a formal violation of the neuron doctrine established by Ramon y Cajal (see Chapter 2). Yet, the spirit of the neuron doctrine is not challenged by gap junctions as the neuron is clearly the fundamental unit of the nervous system.

than apposing membranes at a chemical synapse. The hemichannels from adjacent cells align to form a pore that is up to 2 nm in diameter (see Box 8-17). Through this pore, ions travel down their electrochemical gradients.

Gap junctions often occur in association with chemical synapses, giving rise to **mixed electrical-chemical synapses**. Although gap junctions exist in neurons of the retina, inferior olive, hypothalamus, cerebellum, thalamus, and cerebral cortex, as well as in astrocytic glia, their contribution to normal CNS function remains poorly understood. This stems in large part from the absence of neurological diseases that are the primary result of connexin mutations in the CNS. From this fact, one may conclude, probably incorrectly, that gap junctions contribute relatively little to brain function. Yet the expression of connexin mutations in the periphery, in both non-neuronal tissues such as the lens and neural tissues such as myelin, are associated with dramatic clinical problems (see Box 8-18).

COMMUNICATION OCCURS AMONG NEURONS USING DIVERSE MECHANISMS

The picture presented here is of a presynaptic element releasing neurotransmitter to send a message to a postsynaptic element, which receives the message using a receptor for the released neurotransmitter. Even considering the very large number of neurotransmitters and the even larger number of receptors, this version of synaptic transmission oversimplifies neural communication in several respects:

- As mentioned in Chapter 7, many neurons release multiple neurotransmitters.
- Cells that are postsynaptic in the classical sense, meaning they express receptors but do not contain synaptic vesicles, may release neurotransmitters such as NO, leading to the term *retrograde signaling* for communication emanating from the “postsynaptic” element.

Box 8-18

CONNEXIN MUTATIONS UNDERLIE CONGENITAL NEUROLOGICAL DISEASES.

A variety of mutations impair or completely knock out the function of connexins, the proteins that make up gap junctions. When the connexins present on myelin are affected, demyelination results (see Chapter 5). In fact, the most common gap junction-related disease involves peripheral demyelination caused by an inherited mutation; inherited demyelination diseases comprise the largest group of the

heterogeneous set of Charcot-Marie-Tooth syndromes (see Box 5-5). **Deafness** is another common result of certain connexin mutations. Connexin mutations prevent supporting cells in the **stria vascularis** of the cochlea (see Chapter 17) from sharing nutrients and distributing potassium ions, resulting in cochlear sensory cells’ dying and consequent deafness.

- Neural elements on both sides of a chemical synapse express receptors. Neurotransmitter binding to presynaptic receptors often regulates subsequent neurotransmitter release or even the packaging of neurotransmitters within vesicles within the presynaptic terminal.
- As mentioned above, many synapses are mixed with both electrical and chemical components.
- Many, possibly most, postsynaptic elements express multiple types of receptors.
- The structural arrangement of synapses, with some located more proximally, or closer to the cell body, than others, weights the inputs arriving at different synapses.

From the diverse mechanisms at each step of the synaptic process arises an enormous repertoire of potential messages that can be sent and received. The diversity in neural communication exists across different synapses and also across time, so that a single synapse may operate differently at different times. The plasticity of synaptic function resulting from experience is the fundamental component of learning.

THE OUTCOME OF SYNAPTIC ACTIVITY DEPENDS ON THE CONNECTIVITY OF THE CELLS INVOLVED

At each stage of our simplified synaptic communication, there is a critical output that serves as the input to the next stage in synaptic communication:

- A membrane potential reaches the threshold for an action potential.
- An action potential elicits calcium influx in a synaptic terminal that then triggers fusion of a synaptic vesicle and release of neurotransmitter.
- Neurotransmitter activates a receptor and thereby causes a change in the electrical properties and/or in the second-messenger status of the cell.

Yet, even if we knew everything about each of these steps, we still could not predict the effect of the communication. To understand the result of synaptic communication, we need to understand the *identity* and *connectivity* of the neurons involved. The same pattern of action potentials sent from a neuron that innervates the cochlea or from a neuron that innervates a skeletal muscle conveys two vastly different messages. Therefore, we now embark on a tour of the basic connections of the human nervous system.



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SECTION 3: NEUROANATOMY

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CHAPTER 9

SPINAL CORD: CONDUIT BETWEEN BODY AND BRAIN

PATHWAYS FOR VOLUNTARY MOVEMENT AND SOMATOSENSORY PERCEPTION TRAVERSE THE LENGTH OF THE NERVOUS SYSTEM

Like real estate, neuroanatomy is all about location, location, location. And just as major thoroughfares provide a better framework than one-block, dead-end alleys for learning the layout of a city, long brain “highways” are key to navigating through the nervous system. Therefore we will follow three long pathways in the central nervous system (CNS) that traverse nearly the entire length of the neuraxis:

- The light touch, vibration, and proprioceptive pathway or dorsal column-medial lemniscus pathway
- The pain and temperature pathway, known as the spinothalamic pathway or anterolateral system
- The corticospinal pathway for voluntary movement

The dorsal column-medial lemniscus and spinothalamic pathways are **sensory** pathways, communicating sensory information from the body, into the CNS and up the neuraxis, to the brain (Fig. 9-1). The corticospinal tract is a **motor** pathway, meaning that it carries information from the cerebral cortex, down the neuraxis, to motoneurons that control contraction of skeletal muscles. *Each of these pathways begins on one side and ends on the opposite or contralateral side.* Knowing where each pathway crosses is essential to deciphering the location of a lesion from the symptoms observed.

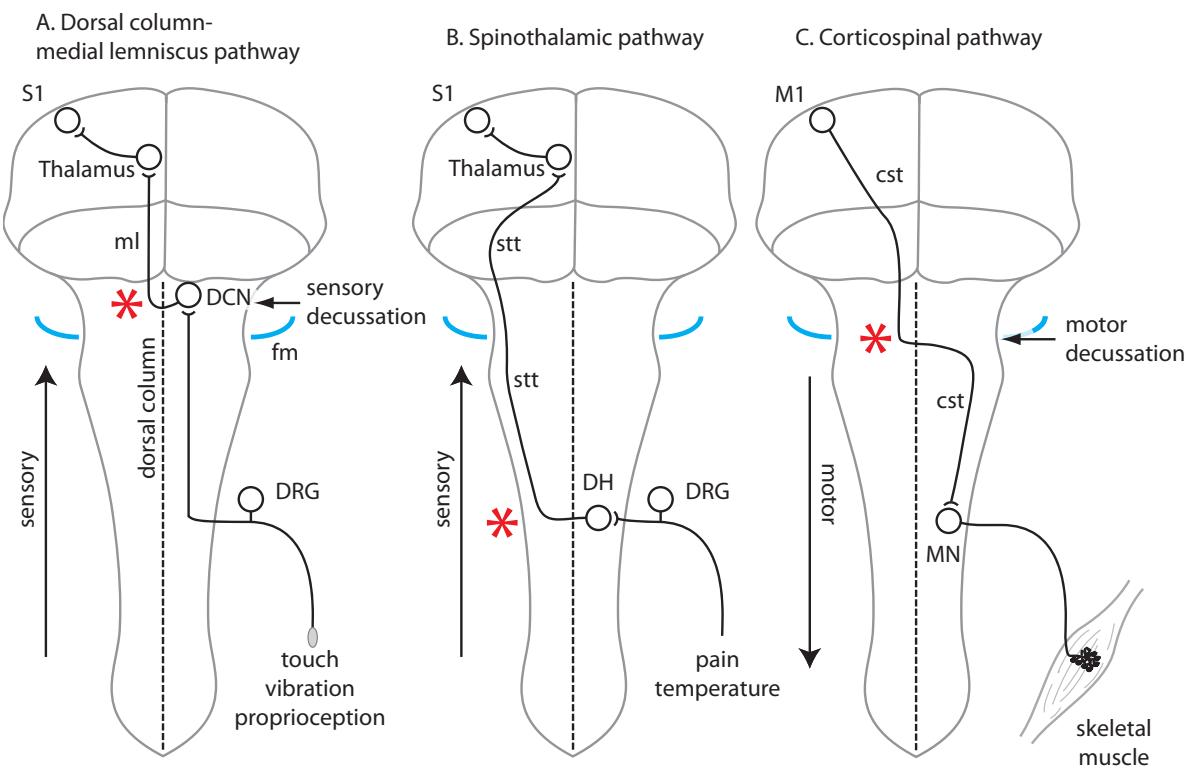


Figure 9-1. The three longest pathways in the human nervous system are illustrated on schematics of the brain and spinal cord viewed from the back. Note that the schematics are stretched horizontally for illustrative purposes. The dotted line in the spinal cord and caudal medulla marks the midline. The foramen magnum (*fm*) separating the spinal cord, below, from the brain, above, is indicated by the blue arcs. **A:** The dorsal column-medial lemniscus pathway carries information about touch, vibration, and proprioception from the body to the contralateral cerebral cortex. Primary afferents, often with encapsulated ends, located in dorsal root ganglia (DRG) transmit tactile information from the periphery all the way to the dorsal column nuclei (DCN) in the medulla. Within the spinal cord, these primary afferents travel in the ipsilateral dorsal column of the spinal cord. Cells in the dorsal column nuclei, located in the medulla, receive input from primary afferents and in turn project to the contralateral thalamus. To reach the thalamus, dorsal column nuclear cells send their axons across the midline. The crossing of dorsal column nuclear axons marks the sensory decussation. When the dorsal column nuclear axons reach the contralateral side, they take a turn to travel rostrally through the brainstem as the medial lemniscus (*ml*). Thalamic cells project to primary somatosensory cortex (*S1*). **B:** The spinothalamic pathway carries information about pain and temperature from the body to the contralateral cerebral cortex. Primary afferents that innervate the periphery as free nerve endings have cell bodies located in the dorsal root ganglia. They transmit information from the periphery to the dorsal horn (DH) of the spinal cord. Cells in the dorsal horn send an axon across the midline to travel rostrally in the spinothalamic tract (*stt*) all the way to the contralateral thalamus. Thalamic cells receiving input from the spinothalamic tract project to primary somatosensory cortex. **C:** The corticospinal pathway originates in the primary motor cortex (*M1*). Cells in primary motor cortex send an axon through the corticospinal tract (*cst*) to contralateral motoneurons (MN) in the spinal cord. At the spinomedullary junction, corticospinal tract fibers cross the midline, marking the motor decussation. Motoneurons that receive input from the corticospinal tract innervate skeletal muscle, required for voluntary movement. All three pathways cross the midline, at sites marked by the red asterisks. As a result, the cerebral cortex on one side is responsible for both voluntary movement and somatosensory perception of the other side of the body. The dorsal column-medial lemniscus pathway crosses the midline in the caudal medulla. The corticospinal pathway crosses at the spinomedullary junction, and the spinothalamic pathway crosses within the spinal cord at the level of the primary afferent input.

THE SPINAL CORD AND SPINAL NERVES SERVE THE BODY

The spinal cord and spinal nerves serve sensory and motor functions involving the body. Sensory information arising from the limbs, trunk, shoulders, neck, and back of the head enter through spinal nerves to spinal cord segments. Muscles of the limbs and trunk are controlled by spinal motoneurons that send their axons out through spinal nerves. In contrast, sensory and motor functions

Box 9-1

SPINAL NERVES EXIT THE VERTEBRAL COLUMN AND CRANIAL NERVES EMERGE FROM THE SKULL.

A *nerve* is a group of axons that travels in the periphery, outside of the environs of the central nervous system, in contrast to *tracts*, which are axonal bundles that travel within the central nervous system (CNS). Nerves that exit the CNS at the level of the vertebral column are called spinal nerves, whereas nerves that exit at the level of the skull are termed cranial nerves. Spinal nerves carry sensory fibers that will terminate in the spinal cord and motoneuron axons that arise from the spinal cord. Similarly, the brainstem is the target of sensory fibers carried in cranial nerves and the source of nearly all motoneuron axons that travel in cranial nerves. There is one exception to this rule. A group of motoneurons present in the spinal cord send their axons into the skull and then out of the skull as cranial nerve XI (see Chapter 10). This exception highlights that nerves are either spinal or cranial depending on their point of exit rather than the site of their origin or termination.

of the head and face are served by *cranial nerves* (see Box 9-1). Sensory input from the face, top of the head, oral and nasal cavities, and the upper airways enters the brainstem via cranial nerves. Motoneurons that send their axons through cranial nerves control muscles involved in producing facial expressions, chewing and swallowing, speech articulation, and some neck and shoulder movements. Both spinal and cranial nerves carry sensory information from and motor information to internal organs such as the heart, pancreas, and colon. Consequently, both the spinal cord and brainstem are involved in visceral sensation and autonomic motor control.

PATHWAYS FOR SENSATION AND VOLUNTARY MOVEMENT CROSS FROM ONE SIDE TO THE OTHER

Light touch, vibration, and proprioception—the sense of the body's position in space—arrives in the brain through the dorsal column-medial lemniscus system. Input comes into the spinal cord from spinal nerves and ascends through the *dorsal columns* of the spinal cord to the *dorsal column nuclei* in the medulla. Note that some refer to the dorsal columns as the *posterior columns* (to remind yourself why this is so, see Fig. 1-4). Cells in the dorsal column nuclei send axons across the midline to ascend through a tract called the *medial lemniscus* to the thalamus. Because it crosses or *decussates*, the dorsal column-medial lemniscus system ends in the brain on the opposite side from the part of the body stimulated. The crossing of dorsal column nuclear cells is often referred to as the *sensory decussation*. Thalamic neurons then ascend to reach primary somatosensory cortex. In sum, the dorsal column-medial lemniscus system carries tactile, vibratory, and proprioceptive information from the body to the contralateral cerebral cortex.

Pain and temperature information from the body surface, muscles, bones and internal viscera travels up the *neuraxis* through the spinothalamic tract. Pain and temperature information comes in from spinal nerves that synapse on neurons in the ipsilateral, or same-side, spinal cord. The spinal cells send an axon across the midline to ascend through the spinothalamic tract to the thalamus. The spinothalamic tract travels in the ventrolateral quadrant of the spinal cord. Recall that in the human spinal cord anterolateral is synonymous with ventrolateral. Therefore, the spinothalamic pathway is also termed the *anterolateral system*, most frequently so in the clinical literature. Thalamic neurons then carry information to primary somatosensory cortex. Pain perception involves both sensory-discrimination—the what, where, and when of a stimulus—and affective—the emotional and motivational reaction evoked by a stimulus—components. The anterolateral system, which ultimately reaches primary somatosensory cortex, is primarily involved in the sensory-discriminative rather than the affective component of pain.

The corticospinal tract consists of axons arising from a set of neurons with cell bodies in the cerebral cortex, primarily in the primary motor cortex of the frontal lobe. The axons of the corticospinal tract travel through the forebrain,

midbrain, and pons, and then through the **pyramids**, two parallel columns running down on either side of the ventral medullary midline. For this reason, the corticospinal tract is also termed the **pyramidal tract**. Corticospinal tract axons cross the midline at the junction of the spinal cord and the medulla and travel down the spinal cord, where they contact motoneurons that control voluntary movements of the legs, trunk, and arms. Because it decussates, *the corticospinal tract starts in the brain on the opposite side from the muscles whose movement it ultimately influences*. The point where the corticospinal tract fibers cross is often termed the **motor decussation**.

The **corticobulbar tract** forms an analogous pathway to the corticospinal tract, controlling voluntary movement of the face, shoulders, neck, jaw, tongue, and upper airway. However, because motor centers targeted by the corticobulbar tract are located in the brainstem, the corticobulbar tract traverses a much shorter distance and correspondingly is affected by lesions in a far more restricted area than is the corticospinal tract. As detailed further in Chapter 23, the corticobulbar tract differs from the corticospinal tract in another respect: it does not uniformly cross, so that movements controlled by the tract are often either bilateral or ipsilateral to the site of origin.

This simple overview (Fig. 9-1) provides enough information for even the beginning student to estimate the likeliest location of a lesion when presented with symptoms. We will consider two examples. First, consider someone who cannot feel anything—pain, temperature, or touch—on the right side of her body, nor can she move the muscles on the right side of her body. One possibility is that all of the spinal nerves have suddenly failed altogether. This is possible, and yet it is unlikely. Thus, a person who can neither feel nor move one side of the body probably has a *central* rather than a peripheral lesion. Knowing just the information provided here, the reader can substantially narrow down the potential location of the lesion to brain or spinal cord and to left or right. The reader should try to solve this before reading the spoiler below.

Since the spinothalamic and dorsal column-medial lemniscus pathways serving one side of the body only travel together above the level of the medulla, the lesion must be above the decussation of the dorsal column-medial lemniscus pathway, the sensory decussation. Since both sensory pathways carrying information about the right side of the body and the corticospinal tract carrying motor information to muscles on the right all travel through the *left* forebrain and brainstem, the lesion is likely to be on the left, at a point above the sensory and motor decussions.

In a second example, consider someone who shows a loss of temperature sensation and a diminution of tactile sensitivity throughout the body, bilaterally, while having intact motor function. No single lesion could produce this constellation of symptoms since temperature information from the left body and temperature information from the right body travel on opposite sides of the spinal cord and on opposite sides of the brain. Although it is possible that the brain suffers perfectly symmetrical damage, it is exceedingly unlikely. Therefore, bilateral impairment of sensory or motor function usually results from a *systemic disease* rather than a focal anatomical lesion. In fact, patients with **Hansen disease**, commonly known as leprosy, often **present**, or first seek medical attention, with a loss of temperature and touch sensation caused by a systemic loss of sensory nerve function.

As we make our way through the nervous system from the periphery to the spinal cord, brainstem, and eventually the forebrain, we will always note the location of each of the three long pathways.

SPINAL NERVES CONTAIN A MIX OF AXONS WITH SENSORY, SKELETAL MOTOR, AND AUTONOMIC MOTOR FUNCTIONS

Spinal nerves contain axons serving a mixture of functions: somatosensory, viscerosensory, somatomotor, and autonomic motor. Somatosensory afferents bring information from the skin, muscles, and bones to the spinal cord, whereas viscerosensory afferents carry signals related to the status of internal organs. The somata of both types of spinal afferents sit in the **dorsal root ganglia**, and the axons of these cells enter the spinal cord through the **dorsal roots** (Fig. 9-2). Motoneuron and autonomic motor neuron axons emanate from neurons in the spinal cord, traveling through the **ventral roots**, to control voluntary and automatic motor functions, respectively. A dorsal root and a ventral root join to form a **peripheral nerve**. Spinal nerves have two main **rami** or branches. The **primary ventral ramus** (ramus is the singular form of rami) travels laterally and ventrally to supply most of the skin,

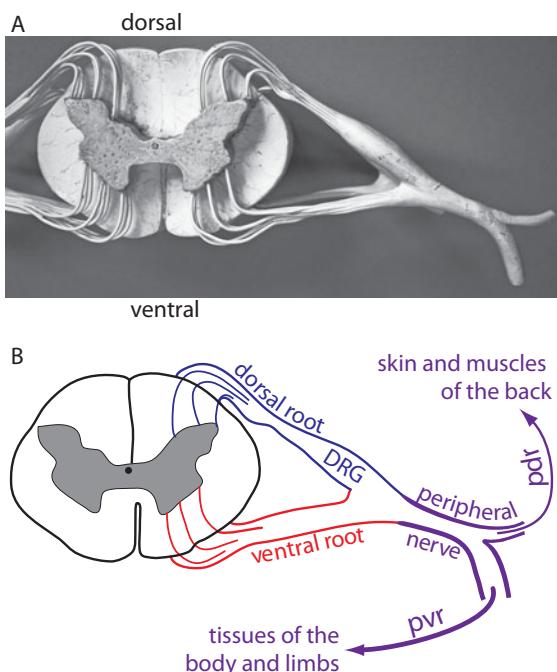


Figure 9-2. The organization of the spinal cord is stereotyped with sensory processing occurring dorsally and motor processing ventrally. Each segment has a bilateral pair of **dorsal roots** and a bilateral pair of **ventral roots**. Primary afferent neurons whose cell bodies are in the **dorsal root ganglia (DRG)** collect information from skin, muscles, joints, bone, tendons, and viscera, and then carry this information into the spinal cord through the dorsal root. Motoneurons send their axons out through the ventral root to skeletal muscles. Autonomic motor neurons also send axons out the ventral root but to autonomic ganglia. As peripheral nerves contain both sensory fibers en route to the dorsal roots and motor fibers emanating from the ventral roots, they serve a mixture of motor, sensory, and autonomic functions. Spinal nerves divide into a small branch or ramus called the **primary dorsal ramus (pdr)** that innervates the skin and muscles of the back and a **primary ventral ramus (pvr)** that serves most axial and limb tissues.

Photograph in A reprinted by permission of Bruni, J.E., and Montemurro, D. *Human neuroanatomy: A text, brain atlas, and laboratory dissection guide*. New York: Oxford University Press, 2009.

muscles, viscera, and other tissues of the body and all of the tissues of the limbs. The smaller **primary dorsal ramus** travels dorsally to supply the skin and muscles of the back.

AUTONOMIC MOTOR CONTROL IS ACHIEVED THROUGH A TWO-NEURON PATHWAY

Spinal autonomic motor neurons are the first of a two-neuron chain that controls autonomic target tissues. The autonomic motor neuron is the **preganglionic neuron**. From the soma within the CNS, a preganglionic neuron sends an axon through the ventral roots, just like motoneurons. However, preganglionic autonomic neurons synapse on neurons in autonomic ganglia rather than on skeletal muscle, as is the case for motoneurons. The autonomic ganglionic neuron is the second neuron in the autonomic control chain, and it sends **postganglionic axons** to autonomic targets throughout the body. There are three types of autonomic target tissues:

- Smooth muscle forms a layer around many internal organs such as blood vessels, the bladder, bronchi, and intestines. Smooth muscle also is present in the eye, around the pupil and lens, eyelid, and skin where it is attached to hair follicles. Contraction of these smooth muscles modifies pupillary diameter, changes the shape of the lens, lifts the eyelid, and produces goose bumps, respectively.
- Cardiac muscle is the striated muscle that makes up the heart.
- Glands are organs that secrete substances such as tears, mucus, sweat, saliva, ear wax, and so on.

There is one exception to the two-neuron chain rule of autonomic motor control. The adrenal medulla, which releases epinephrine during periods of stress or arousal, receives direct innervation from autonomic motor neurons. However, if one considers adrenal medullary cells to be atypical autonomic ganglion cells—both are neural crest-derived—then the pathway that controls adrenal medullary secretion can be viewed as a two-neuron, autonomic control pathway.

SENSORY AND MOTOR AXONS CARRIED IN NERVES ARE DISTINCT FUNCTIONALLY AND MOLECULARLY

Axons within a peripheral nerve belong to more than a dozen functionally and molecularly distinct neuronal types. As we shall see in Chapter 21, distinct types of motoneurons innervate different types of skeletal muscle fiber. Peripheral nerve also contains the axons of both pre- and post-ganglionic

autonomic neurons. Sensory afferents are heterogeneous and include **mechanoreceptors** that respond to nondamaging or **innocuous** mechanical stimulation such as touch, **nociceptors** that respond to **noxious** or tissue-damaging stimuli, and **thermoreceptors** that respond to temperature changes (see Box 9-2).

An important way in which the many types of peripheral fibers differ is in the diameter or **caliber** of their axon, the thickness of the surrounding myelin, and the speed of action potential conduction (see Chapter 5). All three of these factors are related. Axons with diameters of less than 1–2 μm lack myelin altogether and conduct action potentials at very slow rates, less than 2 m/s; these axons are called **C fibers**. Although C fibers are not individually wrapped in myelin, bunches of C fibers are loosely surrounded by a myelin sheath. Myelin wraps each individual axon with a diameter greater than 2 μm . Conduction velocity increases with increasing axonal caliber and a corresponding increase in myelin thickness. Myelinated fibers, or **A fibers**, are divided into three categories based on fiber caliber, thickness of myelin, and conduction velocity:

- **A α :** the most heavily myelinated fibers conduct at the fastest rates, 70–150 m/s
- **A β :** moderately myelinated fibers conduct at moderate rates, 30–70 m/s
- **A δ :** lightly myelinated fibers conduct at slow rates, 5–30 m/s

Box 9-2

NEUROPATHIES ARE A HETEROGENEOUS GROUP OF SYNDROMES THAT INVOLVE THE IMPAIRMENT OF PERIPHERAL NERVE FUNCTION.

Damage to peripheral nerve fibers causes a **neuropathy**. The symptoms of neuropathies depend on the type or types of peripheral fibers damaged. Traumatic injury, meaning damage due to physical impact, tearing, or crushing, of a peripheral nerve typically damages nerve fibers of all types, motor and sensory, that innervate tissues distal to the site of trauma. In contrast, certain diseases target peripheral nerve fibers with a particular molecular signature or metabolic vulnerability. For example, the hyperglycemia and plasma hyperosmolality present in **diabetic** patients can selectively damage myelinated sensory fibers, resulting in **dysesthetic** sensations of numbness, tingling, and pain. Dysesthesia simply means that the sensation perceived is inappropriate for the situation. For example, feeling pain in response to a

light touch or feeling pins and needles in the absence of any stimulation are both dysesthesias. People with a **hereditary sensory and autonomic neuropathy** (HSAN) fail to develop nerve fibers with one or a few specialized functions. HSAN syndromes involve the loss of small-diameter fibers that share a common molecular vulnerability to developmental misprogramming. The loss of small-diameter nociceptors and thermoreceptors results in the patient's inability to sense pain and temperature, whereas the loss of small-caliber autonomic fibers results in patients' inability to sweat, a condition termed **anhidrosis**. Patients with such a **congenital insensitivity to pain** present when they suffer injuries without crying or during teething at the latest, when parents discover that their child has chewed off a digit.

Each functional type of axon belongs to one of the fiber categories, A α , A β , A δ , or C. At the fast extreme, motoneuron axons and proprioceptive sensory axons from muscles and joints are A α fibers. A β fibers carry information about vibration, hair-bending, and texture discrimination, whereas A δ and C sensory fibers carry information about or **code** for pain, temperature, and crude touch. Preganglionic autonomic fibers conduct action potentials at speeds in the 50–70 m/s, whereas postganglionic autonomic fibers are unmyelinated C fibers and therefore conduct action potentials very slowly.

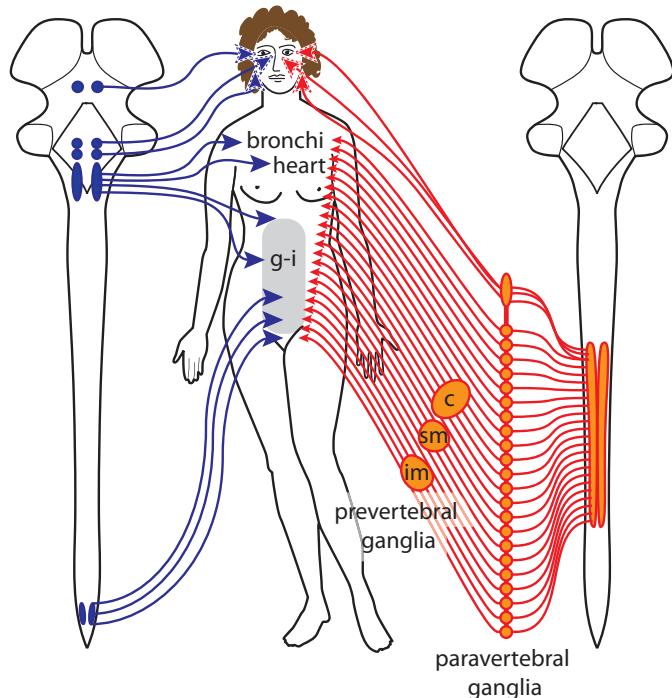
Consider the implications of axons with varied conduction velocities. For a woman of about average height (5' 5" or 1.65 m), an action potential travelling along an A β fiber from the big toe to its destination in the fifth lumbar segment of the spinal cord will require roughly 10 ms, whereas an action potential carried in a C fiber nociceptor from the big toe would take *more than a second* just to reach the spinal cord. As will be discussed fully in Chapter 22, the very rapid conduction of action potentials in *all* movement-serving fibers, both sensory fibers serving proprioception and motor fibers innervating skeletal muscles, enables the immediate correction of movements when unexpected obstacles are detected by fast-conducting sensory fibers. In contrast, as everyone can relate to from having stubbed their toe, a noticeable delay intervenes between the impact of a noxious stimulus onto the big toe and the perception of greatest pain. Although it may appear counterintuitive that nociceptors conduct action potentials so slowly, one may imagine that the extra investment of myelin needed for fast conduction is not warranted in the case of cells that are relatively rarely engaged, at least far less often than are motoneuronal and proprioceptive axons.

AUTONOMIC NEURONS BELONG TO EITHER THE SYMPATHETIC OR PARASYMPATHETIC DIVISION

There are two different types of autonomic neurons, which belong to two different divisions of the autonomic nervous system: **sympathetic** and **parasympathetic** (Fig. 9-3). Although both use a two-neuron chain that takes output from the CNS to target tissues, sympathetic and parasympathetic systems are distinguished by anatomical, pharmacological, and functional properties (Table 9-1).

The sympathetic nervous system is maximally engaged during times of great excitement, arousal, and activity. In contrast, the parasympathetic system is maximally engaged during periods of calm, rest, and recuperation, including during sleep. Preganglionic sympathetic axons exit the thoracic and upper lumbar cord through the ventral roots and terminate in **paravertebral ganglia** that hug the spinal cord or **prevertebral ganglia** found closer to an abdominal target tissue. Preganglionic parasympathetic somata are found both in the brainstem and in the sacral spinal cord, giving rise to the term **craniosacral** as a synonym for parasympathetic. Sacral pre-ganglionic parasympathetic axons exit the sacral cord through ventral roots and terminate in ganglia situated in or very close to the target tissues, which include the hindgut and organs of the pelvic floor, such as the bladder.

Parasympathetic



Sympathetic

**VIRTUALLY
EVERY
PHYSIOLOGICAL
FUNCTION IS
MODULATED
BY AUTONOMIC
NEURONS**

Figure 9-3. Nerves of the parasympathetic or craniosacral system (*left*) emerge from the brainstem and the sacral cord. Long axons travel to parasympathetic ganglia that are in or near the final target tissue. Targets of the parasympathetic system include the lens, pupillary constrictor, and lacrimal and salivary glands within the head and the viscera of the body, including the gastrointestinal tract (*g-i*). The cranial contribution to the parasympathetic system reaches most of the viscera except the hindgut, bladder, and sexual organs, which are influenced by preganglionic parasympathetic neurons in the sacral spinal cord. Nerves of the sympathetic system (*right*) emerge only from the thoracic and upper lumbar cord. Preganglionic sympathetic axons travel either to paravertebral ganglia or to prevertebral ganglia. Paravertebral ganglia lie in a line called the **sympathetic chain** that is situated just ventrolateral to the vertebral column. Prevertebral ganglia located in the abdomen include the celiac (*c*), superior mesenteric (*sm*), and inferior mesenteric (*im*) ganglia. From sympathetic ganglia, post-ganglionic axons travel relatively long distances to target tissues. Note that sympathetic innervation of the adrenal medulla is direct and does not involve a ganglionic neuron (not shown). Targets of the sympathetic system include the eyelid, pupillary dilator, and lacrimal and salivary glands within the head and the viscera of the body. Beyond these targets, the sympathetic system also innervates sweat glands and cutaneous blood vessels all over the body. Interruption of the sympathetic innervation of the eye, arising from preganglionic neurons in the upper thoracic cord, causes Horner syndrome (see Box 9-3).

sympathetic activation largely oppose the effects of sympathetic activation. Energy is channeled into digestion and away from skeletal motor activity. Secretion of mucus, saliva, and tears is promoted. In sum, the sympathetic system promotes arousal and skeletomotor action, whereas the parasympathetic system promotes rest, inactivity, and digestion.

In many tissues, the effects of sympathetic and parasympathetic inputs are opposing. We saw an example of this in Chapter 8: parasympathetic input to the sinoatrial node slows heart rate, whereas sympathetic input speeds up heart rate. Similarly, sympathetic input results in pupil dilation, and parasympathetic activity produces pupillary constriction. Although the sympathetic and parasympathetic

TABLE 9-1. THE SYMPATHETIC AND PARASYMPATHETIC BRANCHES OF THE AUTONOMIC NERVOUS SYSTEM DIFFER IN THEIR ORGANIZATION, NEUROCHEMISTRY AND FUNCTION

PROPERTY	SYMPATHETIC	PARASYMPATHETIC
Location of preganglionic somata	Thoracic and upper lumbar (T1–L3) cord	Brainstem and sacral cord (S2–S4), thus “ craniosacral ”
Axonal anatomy	Preganglionic axon shorter than postganglionic axon	Preganglionic axon longer than postganglionic axon
Location of autonomic ganglia	Paravertebral and prevertebral sympathetic ganglia arranged in chains and located at some distance from the target tissue	Ganglia located in or very near the target tissue
Ganglionic neuronal transmitter	Mostly norepinephrine except for sympathetic ganglionic neurons innervating sweat glands, which use acetylcholine	Acetylcholine
Circumstances of maximal activation	Engaged maximally during periods of high arousal and excitement including during fights and escapes	Engaged maximally during rest and sleep to promote, growth, digestion, and recuperation

inputs produce opposite outcomes in both of these examples, they do so by different mechanisms. In the case of heart rate, sympathetic and parasympathetic neurons have opposing effects on the same target tissue: the cells of the sinoatrial node. In contrast, in the case of pupillary control, sympathetic and parasympathetic pathways target different muscles: sympathetic neurons control the pupillary dilator muscle, whereas parasympathetic neurons control the pupillary sphincter muscle (see Box 9-3). Both shared and distinct targets for sympathetic and parasympathetic pathways occur.

In some tissues that receive both sympathetic and parasympathetic innervation, the effects of the two inputs are different but not opposing. For example, parasympathetic activation is primarily responsible for tear production both under baseline conditions and in response to the presence of an irritant in the eye. Sympathetic stimulation also increases tear production, albeit far less so than does parasympathetic stimulation. The composition of tears produced by sympathetic and parasympathetic stimulation differs, suggesting that the autonomic regulation of lacrimal glands is more nuanced than simply accelerating or inhibiting tear production. Similarly, sympathetic and parasympathetic inputs appear to alter the composition of saliva, ear wax, nasal secretions, and the like differently. Finally, there are several tissues that do not receive dual innervation. Cutaneous blood vessels, sweat glands, adipose tissue, the adrenal medulla, and the liver only receive sympathetic input.

It should be noted that most of the body receives sympathetic innervation in one way or another. In many cases, sympathetic innervation acts directly on the target tissue. This is the case for the sympathetic innervation of the heart’s sinoatrial node and the eye’s pupillary dilator muscle. However, in other cases, sympathetic nerves exert their effects indirectly through effects on the smooth muscle that controls blood vessel diameter. More sympathetic activity constricts blood vessels, decreasing blood flow to the organ involved, and less sympathetic activity decreases blood vessel constriction,

TABLE 9-2. THE SYMPATHETIC AND PARASYMPATHETIC DIVISIONS INFLUENCE VIRTUALLY EVERY PHYSIOLOGICAL PROCESS

TARGET TISSUE OR PROCESS	SYMPATHETIC	PARASYMPATHETIC
Superior tarsal muscle	Lifts the eyelid during waking and in response to arousing stimuli	—
Ciliary body	—	Makes the lens more spherical, enabling near vision
Pupillary diameter	Dilates the pupil via activation of the pupillary sphincter muscle	Constricts the pupil via activation of the pupillary dilator muscle
Tears	Minor role in tear production, modulates tear composition by promoting protein secretion	Predominant role in tear production
Nasal mucus	Inhibits mucus production and secretion	Stimulates mucus production and secretion
Saliva	Modulates salivary composition by promoting protein secretion	Predominant role in both resting and reflex saliva production, responsible for mucin secretion
Heart rate	Speeds up, increases cardiac output	Slows down, decreases cardiac output
Cardiac stroke volume	Increases, increases cardiac output	Decreases, decreases cardiac output
Coronary arteries	Dilates, increases cardiac output	—
Most arteries and veins, particularly those supplying skin	Constricts, resulting in an <i>increase in blood pressure</i> and a <i>conservation of body heat</i>	—
Arteries to skeletal muscle	Dilates	—
Lung function	Dilates bronchioles, stimulates bronchial gland secretion	Constricts bronchioles
Liver	Stimulates glycogenolysis	—
Pancreas	Decreases exocrine secretion (of gastrin, cholecystokinin, and so on) and islet secretion of insulin and glucagon	Increases exocrine secretion (of gastrin, cholecystokinin, and so on) and islet secretion of insulin and glucagon
Digestive tract: stomach, intestines and colon	Decreases motility, constricts sphincters	Increases motility, increases secretion, and dilates sphincters
Adrenal medulla	Stimulate release of epinephrine and norepinephrine	Increases motility, increases secretion, and dilates sphincters
Bladder	Increases elasticity	Contracts, required for voiding
Sexual function	Promotes sexual arousal, erections	Stimulates orgasm, ejaculation
Sweat glands	Increases sudomotor activity, primarily to promote heat loss	—
Pilomotor	Contracts arrector pili muscles, producing piloerection and goose bumps	—
Adipose tissue	Stimulates lipolysis	—

Listed here are many, but not all, of the physiological processes that are modulated by sympathetic and / or parasympathetic inputs. Blank (—) cells denote either an absence, or a paucity, of innervation from that system. Text in blue denotes cranial nerve pathways. All other pathways employ spinal nerves

HORNER SYNDROME RESULTS FROM THE INTERRUPTION OF THE SYMPATHETIC PATHWAY TO THE EYE.

The sympathetic pathway to the eye starts with preganglionic sympathetic neurons in T1 and T2. The axons of these neurons travel in the sympathetic chain to synapse in the superior cervical ganglion. Ganglionic neurons send a post-ganglionic axon that travels along the carotid artery and ultimately to the eye. Interruption of the sympathetic pathway from the thoracic cord to the eye, anywhere along its length, causes **Horner syndrome**, which consists of **miosis**, or pupillary constriction, and **ptosis**, or drooping eyelid. Miosis and ptosis result from disruption of the tonic sympathetic excitation of two smooth muscles, the pupillary dilator muscle that dilates the pupil and the **superior tarsal** muscle that lifts the eyelid. Facial anhidrosis, or lack of sweating, also occurs in many cases when the sympathetic innervation to facial sweat glands is interrupted. Commonly, Horner syndrome is **iatrogenic**, meaning that it is the unintended result of a medical procedure, such as carotid artery dissection or jugular puncture. Rarely, Horner syndrome is the result of a **Pancoast tumor**, a tumor in the apex of the lung that impinges on sympathetic nerves as they emerge from the thoracic cord.

allowing more blood flow to the organ. In this way, sympathetic nerves can indirectly influence skeletal muscle, brain, cardiac muscle, the abdominal viscera, salivary glands, and so on.

The notion that the sympathetic system serves fight-or-flight and the parasympathetic system serves rest-and-digest overstates the dichotomy between these two divisions of the autonomic nervous system. In fact, the balance between sympathetic and parasympathetic activity is a continuum. This balance varies not only with the moment-to-moment arousal state but also across longer time scales as health status, athletic conditioning, and age change. In young athletes, parasympathetic activity dominates to the extent that elite cyclists in the Tour de France race reportedly have resting heart rates as low as 30 beats per minute. With age, sympathetic activity tends to increase. Although sympathetic nerves are tonically active in all of us, abnormal elevations in **sympathetic nerve activity**, often abbreviated as **SNA**, accompany and may even cause certain cardiovascular pathologies (see Box 9-4).

SENSORY AND MOTOR ROOTS MARK SPINAL SEGMENTS AND COMBINE TO FORM MIXED PERIPHERAL NERVES

The spinal cord is a segmented structure, meaning that the repeating sections of the cord, **segments**, share common characteristics. Each spinal segment gives rise to four roots, bilateral pairs of dorsal and ventral roots. In fact, a spinal segment is defined as the area that gives rise to bilateral pairs of roots (Fig. 9-4A). In the human, the average spinal segment is more than a cm, about a half inch, in length. As axons entering or exiting a spinal segment cross this considerable length of tissue, the axons bundle together into **fascicles**, which fan out as **rootlets**. Dorsal rootlets coalesce into a single dorsal root, which then enters the dorsal root ganglion while ventral rootlets coalesce into a single ventral root. In each segment, dorsal roots carry sensory information into the spinal cord, and ventral roots carry motor information from the spinal cord to the periphery. The roots emanating from each segment join together to form mixed, meaning sensory and motor, peripheral nerves (Fig. 9-2).

Axons of dorsal root ganglia neurons make up the dorsal root and carry sensory input into the spinal cord. The cell body of a dorsal root ganglion neuron sends out only one process, which then bifurcates into a central branch that enters the spinal cord and a peripheral branch, typically much longer than the central branch, which travels toward the target tissue such as skin, muscle, bone, or tendon (see cells marked DRG in Fig. 9-1A,B). The dorsal root ganglion cell sits between the peripheral and central branches, providing biochemical and nutritive support to both. Roots, harbored within the protective sheathing of the dura, are part of the CNS, whereas *the dorsal root ganglia are located at the transition from dorsal root to peripheral nerve and sit just outside the dura*. The dorsal root

ELEVATED SYMPATHETIC NERVE ACTIVITY MAY CONTRIBUTE TO SEVERAL COMMON CARDIOVASCULAR PATHOLOGIES.

Sympathetic nerves are tonically active, but their level of activity changes across time. A portion of sympathetic fibers fire infrequently during rest and many more fibers fire frequently during intense arousal. Collectively, sympathetic fibers are never silent for hours or days at a time. As a consequence, target tissues are influenced by sympathetic nerve activity from birth to death. As the reader knows, sympathetic nerves innervate a large variety of targets. Although all sympathetic nerves may be activated by extremely arousing conditions, tailored sympathetic activity is a more typical occurrence. Tailored responses allow for increases in the nerves supplying selected sympathetic targets, concurrent with decreases or no change in the activity of other sympathetic nerves.

The constant influence of sympathetic nerve activity upon the heart and blood vessels appears to be particularly noteworthy as it accompanies several forms of cardiovascular disease and may even be a contributing pathogenic factor in some cases. Changes in the activity of sympathetic nerves accompany sleep apnea and heart failure. The standard use of pharmacological therapeutics aimed at antagonizing sympathetic influences on the

cardiovascular system in individuals with heart failure suggest that therapeutics aimed at decreasing sympathetic activity may be a useful approach to treatment of additional pathologies involving abnormal sympathetic activity.

Sympathetic nerve activity changes, in terms of both the number of active fibers and firing frequency, across multiple time scales. Moment-to-moment changes occur in response to startle, apnea, or other stressors. Sympathetic nerve activity is also influenced by slower changes such as aging, changes in body mass, hormonal state, chronic stress, and the like. Central homeostatic pathways including pathways originating in the hypothalamus are probably the substrate by which stress and other environmental conditions alter sympathetic output. Interestingly, cloistered nuns, living in a static and unchallenging environment, show no age-related increase in sympathetic nerve activity, suggesting that central influences may in fact be at the root of age-related and environmentally induced increases in sympathetic tone. Such central influences may be at the heart of the improvement seen in cardiac patients who change their lifestyle to include both more physical activity and less mental stress.

ganglia, which derive from neural crest, are part of the peripheral nervous system. This renders neurons in the dorsal root ganglia particularly susceptible to external damage from toxins, viruses, and the like.

The ventral root, carrying motor information from the spinal cord, contains axons—also called fibers—that emanate from motoneurons in the cord and are bound for somatic muscles and autonomic ganglia. Somatic motoneurons that innervate a single skeletal muscle sit together in **pools** that stretch longitudinally across several spinal segments. Therefore, motoneurons from one pool destined for one skeletal muscle exit through several adjacent roots (Fig. 9-4). The axons arising from one motoneuron pool join together within a single nerve. This anatomical arrangement means that an injury to a muscle-supplying nerve is likely to cause far more motor impairment than an injury to a ventral root or rootlet (see Box 9-5).

THE SPINAL CORD HAS A REGIONAL ORGANIZATION RELATED TO THE BODY PLAN

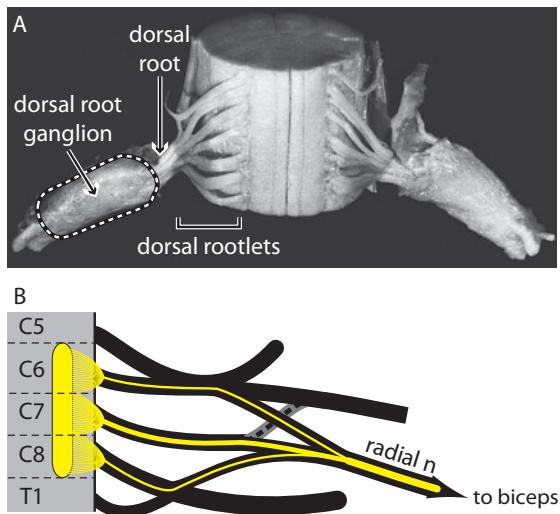


Figure 9-4. A: This photomicrograph shows a single spinal segment viewed from the dorsal side. Dorsal root ganglion neurons send a central process into the spinal cord through the dorsal root. The dorsal root breaks into dorsal rootlets that enter the spinal cord across the length of the spinal segment. The axons of motoneurons bundle into rootlets that coalesce into a ventral horn (not shown). B: This diagram shows a single spinal segment viewed from the ventral side. Note that the photograph in A and diagram in B are views of opposite sides of the cord. A small region of the brachial plexus, the web of nerves that arises from the cervical cord to innervate the arm, is shown. Motoneurons in one pool (*yellow column*) send their axons out through many rootlets and multiple ventral roots. The motoneurons that innervate the biceps are located in three cervical segments, C6–C8, with the majority of the motoneurons in C7. Axons bound for the biceps muscle converge into a single peripheral nerve before reaching their target muscle. Because of this arrangement, interruption of a root or rootlet produces less severe motor symptoms than does interruption of a nerve.
Photograph in A reprinted by permission from Bruni, J.E., and Montemurro, D. *Human neuroanatomy: A text, brain atlas, and laboratory dissection guide*. New York: Oxford University Press, 2009.

Despite their fundamental similarities, segments differ in substantial ways including size, functional components, tissues innervated, and vertebral level at which the roots exit the vertebral column. Indicative of the latter difference in particular, the segments of the spinal cord are divvied into five gross divisions, which are from rostral to caudal (Fig. 9-5):

1. Cranial—Eight segments innervating the back of the head, neck, shoulders, and arms
2. Thoracic—Twelve segments innervating thorax and upper abdomen and providing sympathetic outflow to the body
3. Lumbar—Five segments innervating the pelvic girdle and most of the legs

Box 9-5

VENTRAL ROOT LESIONS PRODUCE LESS SEVERE MOTOR SYMPTOMS THAN DO PERIPHERAL NERVE LESIONS.

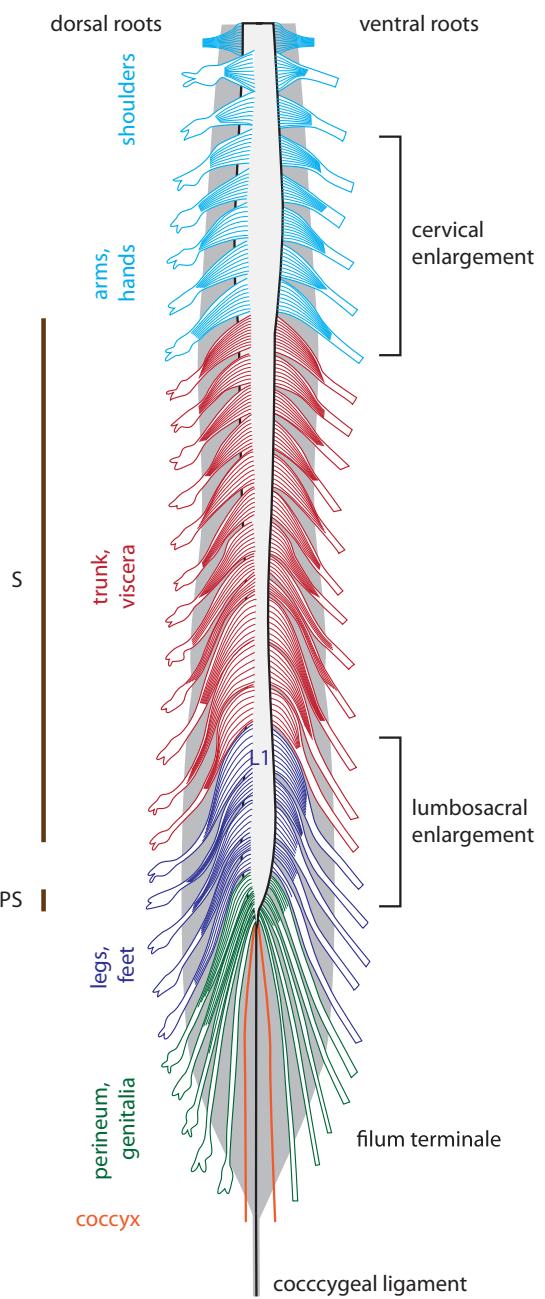
Because the output of each motoneuron pool converges from several roots to a single peripheral nerve (Fig. 9-4), nerve lesions or neuropathies cause more severe motor consequences than do root lesions or **radiculopathies**. Typically, neuropathies cause a complete inability to use a muscle, termed **paralysis**, whereas radiculopathies cause weakness or **paresis**.

The suffix **-plegia** is synonymous with **paralysis** and is typically used with a prefix denoting the

location of the problem. For example, the inability to move one side of the body is referred to as **hemiplegia**. **Paresis** is also used as a suffix, so that weakness on one side of the body is referred to as **hemiparesis**. **Palsy** is an ambiguous term used to refer to either weakness or paralysis. In this book, we use the term **palsy** to refer to injuries which, depending on severity, produce either weakness or paralysis.

Figure 9-5. In humans of average stature, the spinal cord is less than a foot and a half long, just over 40 cm, from the foramen magnum to the conus medullaris, the caudal tip of the spinal cord. It is a segmented structure, meaning that the cord is made up of repeated spinal cord segments. Each spinal cord segment has a stereotyped structure with dorsal roots, leading to dorsal root ganglia, emanating from the dorsal side of the cord (left side) and ventral roots emanating from the ventral side of the cord (right side). Dorsal and ventral roots travel through the dural sleeve (gray region) containing the spinal cord to exit from the vertebral column, often at a location far more caudal than the segment's location. *The location of the spinal segment is at the site where the rootlets emerge from the cord and not where the roots emerge from the spinal column.* For example, the L1 segment is located where the L1 rootlets emerge from the spinal cord. The spinal cord is topographically organized with the most rostral segments serving the most rostral parts of the body and the most caudal segments serving the most caudal parts of the body. Note that the organization of the human spinal cord has evolved from the topography present in quadrupeds, where the perineum and genitalia, and coccyx or tail in some species, are the most caudal structures, *not* the hind limbs. Due to this evolutionary inheritance, the spinal representations of the upper and lower limbs are interposed at the sites representative of where the limbs join the body axis. Generally, cervical segments (light blue) serve the shoulders and arms, and lumbar segments (dark blue) serve the legs, while thoracic segments (red) serve the trunk and sacral segments (green) serve the perineum and genitalia. The cervical enlargement that serves the arms is located from C4 to T1 and the lumbosacral enlargement that serves the legs includes segments from L1 to S3. The locations of preganglionic sympathetic (S) and parasympathetic (PS) neurons are marked by the lines on the left. Since the vertebral column lengthens far more than the spinal cord during growth (see Fig. 9-7), most roots, all but the most rostral ones, must travel caudally to reach the appropriate exit point from the vertebral column. As a consequence, the most caudal portion of the vertebral column contains a large number of spinal roots but no cord. Attaching the spinal cord at the caudal end is accomplished by the filum terminale, a condensation of pia that is invested with dura to form the coccygeal ligament as it leaves the dural sleeve. The coccygeal ligament attaches to the coccyx. In this way, the conus medullaris is anchored to the coccyx by the filum terminale / coccygeal ligament.

Modified with permission from deArmond S., et al. *Structure of the human brain: A photographic atlas*. New York: Oxford University Press, 1989.



4. Sacral—Five segments innervating urogenital and perianal structures and the back of the legs, and providing parasympathetic outflow to the hindgut and pelvic organs
5. Coccygeal—One segment innervating the coccyx or tailbone

Cranial to sacral spinal divisions are abbreviated as C, T, L, and S. The segments are numbered from rostral to caudal, so that C1, the first cranial segment, abuts the medulla, C8 abuts T1, T12 abuts L1, and so on. Topography is the most obvious and complete dissimilarity between segments. Cranial segments innervate structures closer to the head, and sacral segments innervate tissues closer to the tail, or in our case

tailbone. The number and diversity of tissues, as well as the number and diversity of fine movements possible, are far greater with the arms and legs than with the trunk. Therefore, cranial and lumbosacral segments that support arm (C₄–T₁) and leg (L₁–S₃) sensation and movement are enlarged. The widest portion of each enlargement is at the segments that are connected to the most distal parts of the limbs: the hands and fingers (C₇–C₈) in the case of the **cranial enlargement** and the feet and toes (L₅–S₁) in the case of the **lumbosacral enlargement**.

The region of skin from which sensory information reaches a spinal segment is termed a **dermatome**. Throughout the body and parts of the limbs, dermatomes appear as horizontal slices across the body (Fig. 9-6) and largely longitudinal slices of the limbs. It is important to remember that adjacent segments receive sensory information from overlapping parts of skin. Therefore, the functional loss of a single dermatome, as occurs when a dorsal root is lesioned, will only impact a narrow region that is outside of the territory that receives overlapping innervation from adjacent segments (see Box 9-6).

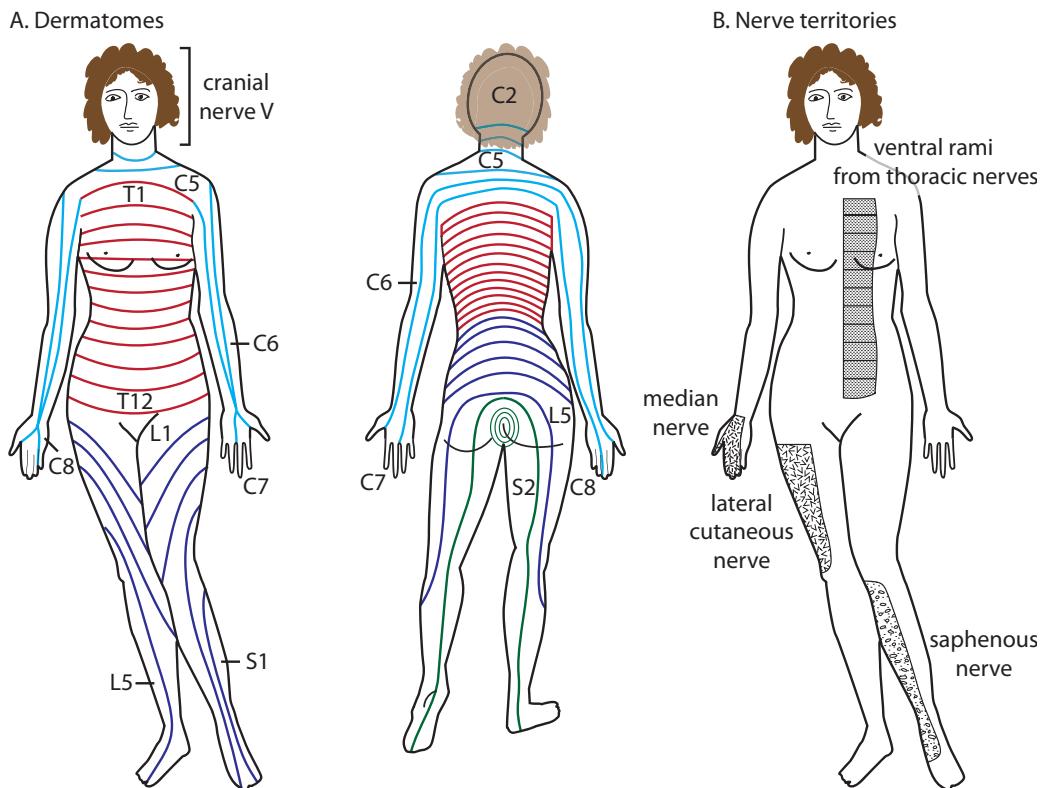


Figure 9-6. **A:** Spinal dermatomes are the cutaneous regions innervated by the sensory fibers of each spinal segment. Note that these territories appear primarily as horizontal slices through the trunk. Dermatomes in the limbs are longitudinal in orientation. However, the limb dermatomes actually share the same orientation as trunk dermatomes in a quadruped. Thus, in a person on all fours, the orientations of the dermatomes in trunk and limbs are roughly parallel. Because of our evolutionary inheritance, the most caudal segments of the spinal cord have dermatomes in the perineum, anus, and coccyx and not in the feet. Note that there is no sensory root in the first cervical segment. The top of the head, face, and oral cavity are innervated by the fifth cranial nerve (see Chapter 10). The innervation of the ear (not shown) is shared by several spinal and cranial nerves with the C₂ dermatome including the back of the ear. **B:** Nerve territories differ substantially from dermatomes in shape and orientation. The few examples illustrated here show that nerve territories can cut across dermatomes. For example, the territory supplied by the median nerve includes parts of dermatomes from segments C₆ to C₈. The territory of the lateral cutaneous nerve includes parts of several lumbar dermatomes. In other cases, particularly in the trunk, nerve territories are substantially smaller than dermatomes. For example, the ventral rami from the thoracic nerves innervate no more than a quarter of the corresponding thoracic dermatome.

HERPES VIRUSES THAT LIVE IN A DORMANT FORM IN DORSAL ROOT GANGLION CELLS CAN RE-ERUPT TO CAUSE A VERY PAINFUL CONDITION CALLED HERPES ZOSTER.

Loss of function in a single dorsal root ganglion causes only a narrow strip of **anesthesia**, or insensitivity to any somatosensory stimulation, because neighboring dorsal root ganglions innervate overlapping regions of skin. On the other hand, positive signs resulting from dorsal root ganglion dysfunction affect a larger cutaneous zone. For example, **herpes zoster** or **shingles** is a disease caused by the **varicella zoster virus** which initially causes **chickenpox**, usually in young children. The virus particles are taken up by sensory neuron terminals and retrogradely transported back to the sensory neuron

somata in the dorsal root ganglia. The virus can remain latent in the dorsal root ganglion neurons for decades. However, latent varicella zoster virus particles can also reactivate. When the virus particles present in a dorsal root ganglion reactivate, they produce a rash that covers the dermatome innervated by the infected dorsal root ganglion; this rash is herpes zoster. Thus, *herpes zoster is a blistering rash contained within a single, unilateral spinal dermatome or a single division of the trigeminal dermatome* (see Chapter 10). This rash is exquisitely painful.

ROOTS FROM PROGRESSIVELY MORE CAUDAL SEGMENTS TRAVEL PROGRESSIVELY LONGER TO EXIT THE VERTEBRAL COLUMN

The C₁ motor root (there is no C₁ dorsal root) exits the vertebral column from between the skull and the first cervical vertebral bone. Roots from successively caudal segments exit through the **intervertebral foramina** between successively caudal pairs of vertebrae (i.e., C₂ roots exit between C₁ and C₂ vertebrae, C₃ from between C₂ and C₃ and so on). However, a wrinkle in this layout arises because there are only seven cranial vertebrae to the eight cranial cord segments. Therefore, the C₈ roots exit from between C₇ and T₁ vertebrae. Then, all thoracic, lumbar, and sacral segments exit between the eponymous vertebral bone and its caudal neighbor (see Box 9-7).

Early in embryonic development, the segments of the spinal cord line up with the vertebral bones and **somites** (see Box 9-8), so that roots from the nascent cord travel laterally from the vertebral column to innervate target tissues (Fig. 9-7). However, the vertebral column and body then grow far more than does the spinal cord. This differential growth has the effect of making the spinal cord and vertebral column out of register. Therefore, in the adult, the spinal cord occupies only the top two-thirds or so of the vertebral column. Because of this, spinal roots, at least those exiting from segments caudal to mid-cervical levels, must travel caudally within the vertebral column to exit through the appropriate intervertebral foramen and reach the tissues they are destined to innervate. For example, the L₅ segment of the cord sits about at the level of the final thoracic

Box 9-7

MOST BACK PAIN MAY NOT INVOLVE ANY DISC PATHOLOGY.

Chronic back pain resulting from a herniated disk or other disk pathology was originally thought to arise from the mechanical impingement of a bulging disc on a nearby root, causing irritation and activation of the component fibers. However, far more people have disc pathology than have severe back pain, and some individuals with severe back pain have no obvious disc pathology. Now, experts widely accept the idea that a large proportion of back pain usually stems from the presence of inflammatory chemicals, such as those leaked from the **nucleus pulposus**, the viscous center of the spinal disc. These inflammatory chemicals not only cause inflammation

but sensitize the responses of sensory neurons to stimulation, so that innocuous stimuli, potentially produced by normal movements, produce extremely painful sensations. Steroids, the most common treatment for acute severe back pain, are effective in reducing inflammatory pain but have unwanted side effects and are contraindicated by a number of common coexisting conditions. New treatment strategies are focused on selectively antagonizing the effects of specific inflammatory chemicals, such as the cytokines **tumor necrosis factor** α or TNF- α and **interleukin-1** (often abbreviated as IL-1).

Box 9-8

SOMITES ARE PARAXIAL MESODERMAL TISSUE SEGMENTS THAT DEVELOP INTO SKIN, SKELETAL MUSCLE, AND BONE.

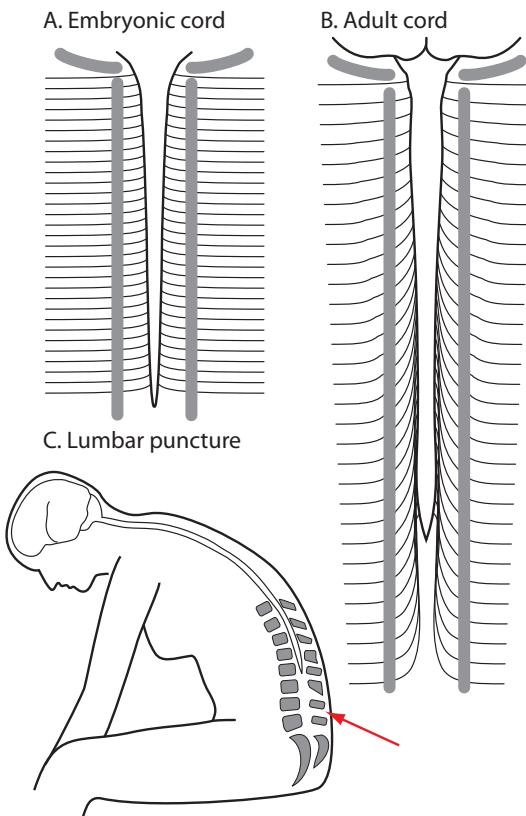
Somites are globular segments of mesodermal tissue that flank the neural tube in the embryo. The somites confer a repeating segmented structure to the dorsal root ganglia and to spinal nerves, which in turn define spinal cord segments. Thus, in the embryo, the roots of one spinal cord segment are connected to the tissues of the flanking somite. Eventually, somites differentiate into three tissue types:

- **Dermatome** or skin
- **Myotome** or skeletal muscle

- **Sclerotome** or axial bones including the vertebral column, ribs, and parts of the skull

Because they differentiate from somites, skin, skeletal muscle, and bone are considered **somatic** tissues. However, somites are not the source of *all* skin, skeletal muscle, and bone in the body. Nonetheless, we use the term *somatosensory system* to refer to the neural pathways involved in sensation from all skin, skeletal muscle, and bone, and the term *viscerosensory* to refer to sensory pathways from the viscera.

Figure 9-7. A: During embryogenesis, spinal cord segments, vertebrae, and the somites from which the segment's targeted tissues develop, all line up. As a result, roots exit from the vertebral column (gray columns) at the level of the segment from which they emerge. However, the spinal cord grows far less than do the bones of the vertebral column and somites. As a result, in the adult (**B**), most roots must travel caudally to exit from the appropriate vertebral level. The roots contained caudal to the conus medullaris form the cauda equina. The cauda equina contains roots from lumbar and sacral segments of the cord but does not contain any spinal tissue. For this reason, clinicians access the subarachnoid space, either to measure the pressure therein or to sample cerebrospinal fluid (CSF), through a lumbar puncture (**C**). In this procedure, a needle is inserted through the dura and into the cauda equina at lower lumbar levels (red arrow).



Box 9-9

PHYSICIANS ACCESS THE CEREBROSPINAL FLUID (CSF) BY INSERTING A NEEDLE INTO THE VERTEBRAL COLUMN BELOW THE LEVEL OF THE CONUS MEDULLARIS.

Lumbar punctures are used to gain access to the CSF in order to obtain a sample of CSF, to measure or relieve CSF pressure, or, less frequently to introduce drugs directly into the central nervous system. In general, sampling CSF and measuring CSF pressure are used as diagnostic tools for meningitis, hemorrhage, hydrocephalus, cancerous growth, and the like.

The technique for lumbar punctures takes advantage of the cauda equina and surrounding

lumbar cistern (Fig. 9-7C). Because the roots of the cauda equina move aside easily, a needle can enter the cistern without risking damage, as would be likely at more rostral levels where the spinal cord is present. Lumbar punctures are typically performed at vertebral level L₄-L₅, where the cauda equina is present, and well below the danger zone where the conus medullaris is present.

DAMAGE TO THE CAUDA EQUINA PRODUCES SERIOUS SYMPTOMS AND CAN BE LETHAL.

Cauda equina syndrome is a dangerous condition involving damage to the roots of the cauda equina. Typically, this syndrome, which can arise from a number of causes including trauma, produces anesthesia within a saddle distribution, meaning the perineum and upper parts of the inner thighs. The most worrisome features of the cauda equina syndrome are urinary retention and constipation, both of which can be fatal if untreated.

CAUDAL AND LATERAL ATTACHMENTS ANCHOR THE SPINAL CORD

The spinal cord and the dural sac surrounding it are firmly attached at the rostral end—to the brain! The spinal cord is continuous with the brain, and the spinal dura is continuous with the brain dura. There are additional attachments from the spinal cord to the spinal dura and from the dura to the vertebral column. These attachments keep the spinal cord in place, with a great deal of flexibility, but still anchored within the body. The **filum terminale**, a coalescence of pia and connective tissue emanating from the conus medullaris, keeps the spinal cord attached to the caudal end of the spinal dural sac. The filum terminale merges with dura to form the **coccygeal ligament**, which anchors the caudal end of the spinal dura to the coccyx (Fig. 9-5). Together, the filum terminale and coccygeal ligament anchor the spinal cord caudally and prevent excessive forward movement of the spinal cord. **Denticulate ligaments** reach from the lateral edge of each segment of the spinal cord to the dura and serve to restrict lateral movement of the spinal cord within the dural sac.

THE SPINAL CORD CONTAINS AN INNER BUTTERFLY OF GRAY MATTER SURROUNDED BY WHITE MATTER

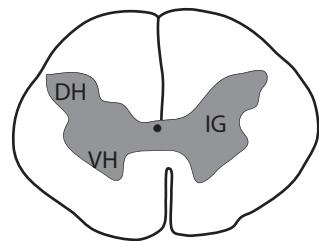
Neurons occupy the central portion of the spinal cord and are surrounded by axonal tracts on all sides (Fig. 9-8). Sensory-related neurons occupy the **dorsal horn**, the dorsal portion of the spinal gray matter, whereas motor-related neurons occupy the **ventral horn**. Primary sensory afferents, with their somata in the dorsal root ganglia, enter the spinal cord through the dorsal roots. Primary afferents carrying information about touch, proprioception, and vibration enter the dorsal columns, bound for the dorsal column nuclei in the medulla. Primary afferents that carry pain and temperature information synapse in the superficial part of the dorsal horn. Motoneurons in the ventral horn send axons out the ventral roots to skeletal muscles.

Axons, traveling up or down the neuraxis, surround the spinal gray on all sides. The spinal white matter is divided up into sections called **funiculi** (singular form is **funiculus**), which are like chimneys (Fig. 9-8C) that house bundles of axons or fasciculi (singular is **fasciculus**). The spinal white matter is divided primarily into dorsal, lateral, and ventral funiculi. The dorsal portion of the lateral funiculus is typically termed *dorsolateral* and the ventral portion termed *ventrolateral*. All long-distance connections, between the spinal cord and brain or between spinal segments, travel in the funiculi surrounding the spinal gray.

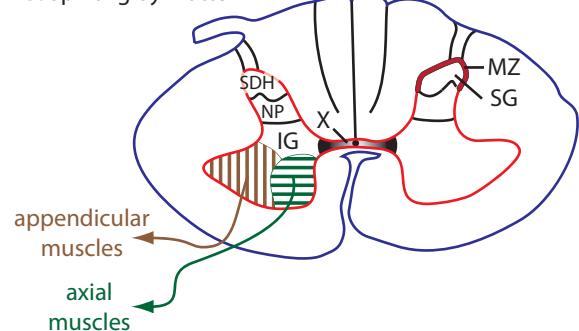
Figure 9-8. A: The spinal cord is divided into a central region of gray matter and a surrounding region of white matter. The gray matter contains the dorsal horn (DH), ventral horn (VH), and intermediate gray (IG) on each side and a midline region around the central canal (X marked in B). B: The dorsal horn contains a superficial region (SDH) that processes pain and temperature information, and a deeper area called nucleus proprius (NP), where tactile information is processed. The superficial dorsal horn is further subdivided into the marginal zone (MZ), which contains neurons that project to the brain and the substantia gelatinosa (SG), where interneurons are concentrated. In the ventral horn, motoneurons are topographically arranged. Motoneurons innervating appendicular, or limb, muscles are present in a lateral extension to the ventral horn, whereas the medial portion of the ventral horn contains motoneurons that innervate axial muscles. C: The white matter of the spinal cord is divided into sections called funiculi (funiculus is the singular form). The dorsal root (dr) carries afferent axons into the spinal cord. Those afferent axons enter the dorsal horn or the dorsal columns (dc), which make up the dorsal funiculus. The dorsal columns contain axons carrying information about touch, vibration, and proprioception. Tactile information arising from the legs travels medially in the fasciculus gracilis (fg) and that from the arms travels more laterally in the fasciculus cuneatus (fc). The lateral funiculus contains the lateral corticospinal tract (lcst) dorsally and the spinothalamic tract (stt) ventrally. The ventral funiculus contains tracts primarily related to axial motor function, such as the ventral corticospinal tract (vcst).

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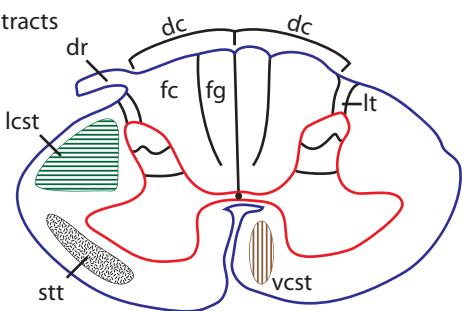
A. Spinal cord cross-section



B. Spinal gray matter



C. Spinal tracts



THE INTERMEDIATE SPINAL GRAY MATTER CONTAINS AUTONOMIC MOTOR NEURONS

Beyond the dorsal and ventral horns, there is the intermediate gray and the central canal region (Fig. 9-8). The intermediate gray contains preganglionic autonomic neurons but only in two regions (Fig. 9-3):

- T₁–L₂ segments contain sympathetic preganglionic neurons.
- S₂–S₄ segments contain parasympathetic preganglionic neurons.

In both cases, the preganglionic neurons are located in the intermediate gray. Sympathetic preganglionic neurons occupy the intermediate gray in a column of cells known of as the **intermediolateral cell column**. The intermediolateral cell column juts out laterally into the lateral funiculus and is so pronounced that it is also termed the **intermediate horn** (Fig. 9-9). The intermediate horn provides an easily recognizable

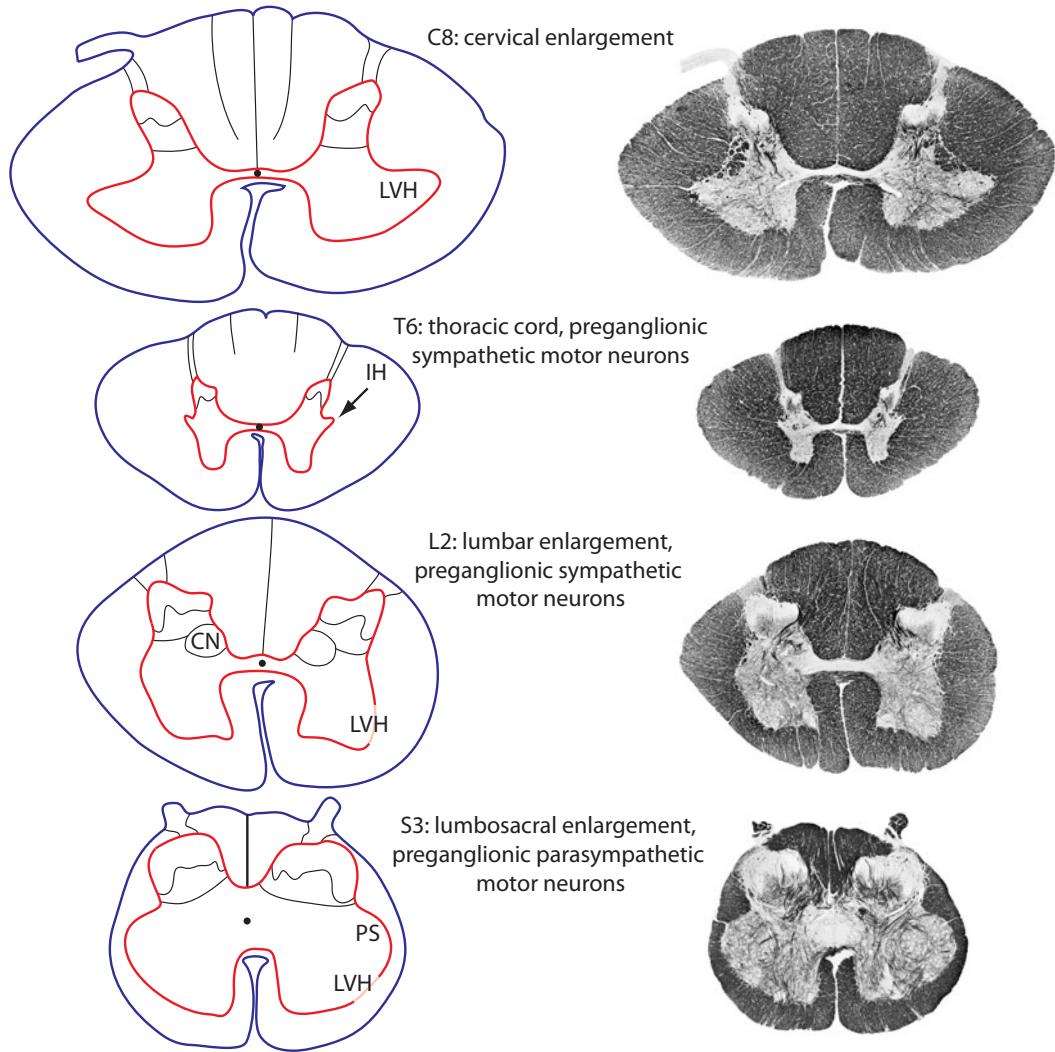


Figure 9-9. The outer shape and internal appearance of the spinal cord differ along the cord's length. Sections from the cervical enlargement (C8) have an elongated oblong shape, a large dorsal horn, a lateral ventral horn (LVH), and a large amount of white matter. Thoracic sections (T6) are small, oblong, have spindly dorsal and ventral horns but a pronounced intermediate horn (IH) containing preganglionic sympathetic neurons. Lumbar sections, L2 is shown here, are roundish in shape, have a large dorsal horn, a lateral ventral horn, and relatively little white matter. In addition, **Clarke's nucleus** (CN), which processes proprioceptive information from the legs bound for the cerebellum, forms a prominent medial bulge in the dorsal horn of segments T12 to L3. The sacral section shown here, S3, is the most caudal part of the lumbosacral enlargement. It is almost square in shape, has a large dorsal horn, a bulging intermediate gray area, a lateral ventral horn, and almost no white matter. Preganglionic parasympathetic neurons (PS) are present in segments S2 to S4 in the intermediate gray. In sum, a few cues can be used to identify the level of a spinal cord section. The cervical cord has the greatest proportion of white matter and the lumbosacral cord the least. Segments from the lumbosacral and cervical enlargements, but not from thoracic cord, contain a lateral ventral horn, reflective of motoneurons that innervate muscles in the distal limb. An intermediate horn marks the thoracic cord.

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marker for thoracic segments. Additional preganglionic sympathetic neurons are found more medially, near the central canal, in an area known of as the **intermediomedial cell column**. In segments S2–S4, the intermediate gray contains preganglionic parasympathetic neurons in a region that is sometimes called the **sacral autonomic nucleus** (Fig. 9-9). Preganglionic parasympathetic neurons send their axons out the ventral roots to parasympathetic ganglia typically located in or very near the ultimate target organ.

THE APPEARANCE OF THE SPINAL SEGMENTS DIFFERS GROSSLY ALONG THE LENGTH OF THE CORD

The different functions of the sacral, lumbar, thoracic, and cervical spinal cord are reflected in markedly different appearances in respective cord segments (Fig. 9-9). The dorsal and ventral horns within the lumbar and cervical enlargements dwarf those of the thoracic cord. This follows naturally from the far greater sensory innervation density and the greater number of muscles in the hands and feet relative to the thorax and abdomen. Corresponding to the greater sensory density in the hands and feet, the dorsal horn in the cervical, lumbar, and sacral cord is extensive, whereas that in the thoracic cord, where sensory function is most rudimentary, is narrow.

Within the ventral horn, *motoneurons that control axial, or trunk, musculature lie medially to those that control limb or appendicular musculature*. To accommodate motoneurons innervating limb muscles, there is an actual lateral extension to the ventral horn, but only in the cervical and lumbosacral enlargements (Fig. 9-9). Thus, thoracic segments contain a narrow ventral horn, located close to the midline, which contains motoneurons innervating axial muscles exclusively. The presence of an intermediate horn is a clear indicator of a thoracic location, whereas the sacral autonomic nucleus is a clear indicator of a sacral segment.

The relative amount of white and gray matter also changes from region to region of the spinal cord. Since all motor tracts descend into the spinal cord and all sensory tracts ascend from the spinal cord, the greatest amount of white matter is located most rostrally in cervical segments. The least amount of white matter is present in the sacral cord and the coccygeal segment. Because of the sensory and motor complexity of the limbs, particularly the arms, relative to the trunk, the largest area of gray matter is found in the cervical enlargement and smallest gray area is found in the thoracic cord. Finally, the outer shape of the cord changes along its rostral to caudal length. Sections from the cervical enlargement have an elongated oblong shape, thoracic sections appear almost diamond-shaped, and lumbar sections appear squat and roundish in shape. Sacral sections are almost square in shape and are instantly recognizable for having almost no white matter.

THE SPINAL GRAY HAS A LAMINATED ORGANIZATION

Superficial, middle, and deep regions of the dorsal horn contribute to different somatosensory functions. The **superficial dorsal horn**, consisting of a thin **marginal zone** overlying the thicker **substantia gelatinosa**, is critical to processing pain and temperature information (see Box 9-11 and Fig. 9-8B). The marginal zone contains most of the neurons that project from the spinal cord to the brain, neurons that are critical to the perception of pain and temperature. The substantia gelatinosa is home to interneurons involved in the processing of somatosensory information,

SPINAL GRAY MATTER HAS HISTORICALLY BEEN VIEWED AS A LAMINATED STRUCTURE.

Bror Rexed, a Swedish neuroscientist, viewed the spinal cord as a laminated structure and introduced a spinal nomenclature that is still used today. Rexed named laminae that correspond to regions of the spinal gray as follows:

- Lamina I: marginal zone
- Lamina II: substantia gelatinosa
- Lamina III–IV: nucleus proprius
- Lamina V–VI: deep dorsal horn
- Lamina VII: intermediate gray
- Lamina VIII: ventral horn interneurons
- Lamina IX: motoneuronal pools

- The region around the central canal was later termed lamina X.

Distinctions between some of Rexed's laminae, for example, laminae III and IV, are difficult to see, and some neuroanatomists argue that there is nothing to see. Furthermore, some of Rexed's so-called laminae are nothing of the sort, meaning they are not layers; the prime example of this is lamina IX, the motoneuron pools that are organized as sagittally oriented cylinders. However, the named regions of the spinal cord—marginal zone, substantia gelatinosa, and so on—are relatively easily delineated, and so this terminology is used here.

especially noxious and thermal stimulation. Deep to the superficial dorsal horn, the **nucleus proprius** processes light touch information. Finally, the deep dorsal horn serves heterogeneous purposes including processing pain, temperature, and viscerosensory input.

The only easily delineated regions within the ventral horn are the motoneuronal pools. As mentioned above, motoneurons innervating a single muscle extend rostrocaudally to form cylindrically shaped pools that cross several segmental boundaries. Motor interneurons fill in the ventral horn around the motoneuron pools. In addition to the intermediomedial and intermediolateral cell columns that contain autonomic motor neurons, the intermediate gray contains a number of reflex-encoding interneurons with roles in transforming sensory input into motor output (see Chapter 22). Finally, the region around the central canal contains viscerosensory cells.

THE THREE LONG PATHWAYS TAKE THREE DIFFERENT COURSES THROUGH THE SPINAL CORD

Now that the reader understands the basic anatomy of the spinal cord, we are ready to follow the routes traveled by the three long pathways (Fig. 9-10). We start with the dorsal column-medial lemniscus pathway. Axons from dorsal root ganglion cells that respond to light touch, vibration, and proprioception travel through the dorsal roots and enter the ipsilateral dorsal funiculus,

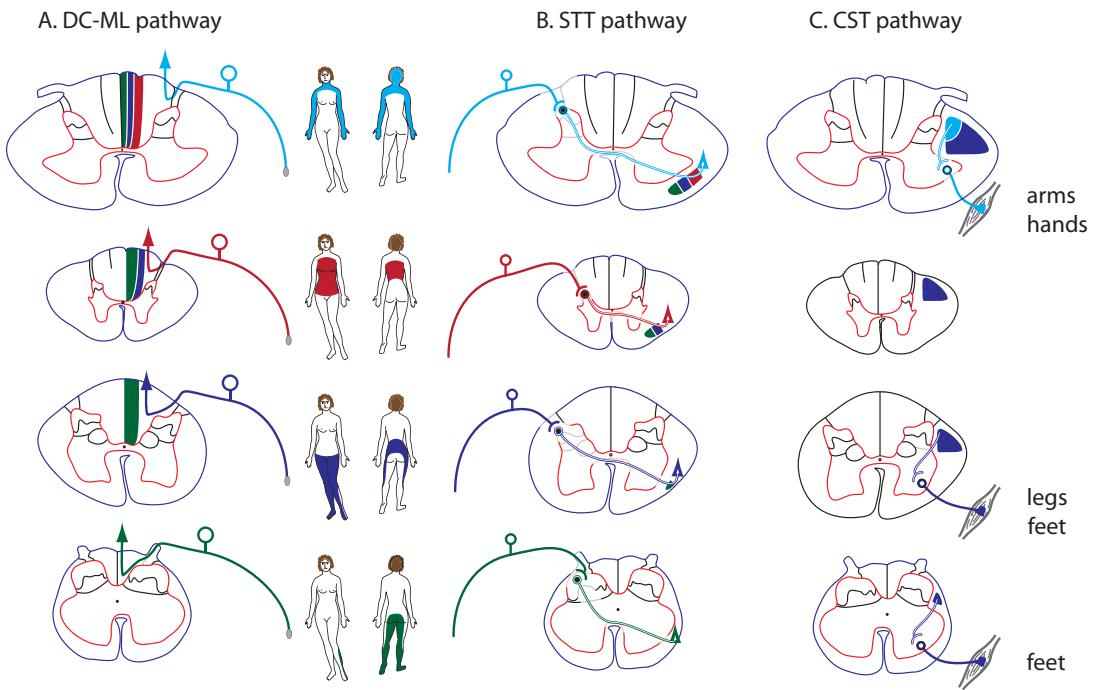


Figure 9-10. A: Dorsal root ganglion cells that code for light touch, proprioception, and vibration send their central process into the dorsal columns. Since afferent input always joins the dorsal columns from the lateral side, legs are represented most medially and arms most laterally. B: Dorsal root ganglion cells that code for pain and temperature send their central process into the dorsal horn to the marginal zone. Cells in the marginal zone send an axon across the midline in the ventral spinal commissure to the contralateral spinothalamic tract, located in the ventrolateral funiculus. C: Corticospinal tract axons that control fine voluntary movements travel in the dorsolateral funiculus as the lateral corticospinal tract. Lateral corticospinal axons leave the dorsolateral funiculus and contact motoneurons in the ventral horn of the cervical and lumbosacral enlargements.

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or dorsal column, to travel rostrally. As axons enter the dorsal columns they take up a progressively more lateral position. Therefore, axons from the most caudal sacral ganglia, carrying input from the perineum, enter and take up the most medial position within the ipsilateral dorsal column. The axons of progressively more rostral dorsal root ganglia, carrying input from the legs, trunks, and arms, take up positions that are progressively more and more lateral within the dorsal columns (Fig. 9-10A). There is a division within the dorsal columns, so that axons carrying tactile information from the legs and most of the trunk travel in the slender **fasciculus gracilis** (from the Latin word for slender), whereas axons carrying the same type of input from the arms and upper trunk travel in the laterally adjacent, wedge-shaped **fasciculus cuneatus** (from the Latin word for wedge, Fig. 9-8C). Together, the fasciculus gracilis and the fasciculus cuneatus comprise a dorsal column. *In sum, each dorsal column carries information about light touch, vibration, and proprioception from the ipsilateral body.*

Axons from dorsal root ganglion cells that respond to pain and temperature travel through the dorsal roots to synapse in the superficial dorsal horn (Fig. 9-10B). Spinothalamic cells located in the marginal zone carry pain and temperature information across the midline through the **ventral spinal commissure**, just ventral of the

Box 9-12

SYRINGOMYELIA PRODUCES A LOCAL INSENSITIVITY TO PAIN AND TEMPERATURE.

Syringomyelia occurs when either a cyst, or a cavity termed a **syrinx** (Greek for pipe or channel), forms around the central canal. The earliest symptom is usually a loss of pain and temperature sensation without any diminution in tactile or proprioceptive sensations. The selective loss of pain and temperature sensation results from the interruption of crossing spinothalamic tract axons. The distribution of sensory loss is dermatomal, from the dermatome of the segment where the damage is located. This results from the fact that spinothalamic tract cells send an axon across the midline, in the ventral spinal commissure, at the same level at which they receive primary afferent input. Syringomyelia most frequently affects cervical and upper thoracic segments.

Most commonly, syrinxes are congenital and are associated **Chiari malformations**. Individuals with a Chiari malformation have an abnormally formed fourth ventricle that pushes out of the cranium and into the spinal column. In many affected individuals, the pressure of the fourth ventricle forms a syrinx around the central canal. Other cases of syringomyelia result when a syrinx forms in reaction to a trauma, infection, or tumor. Neurosurgical treatment is tailored to the cause of syringomyelia. Typically, the aim of surgery is to either relieve the pressure feeding the syrinx or to remove a cyst or tumor.

central canal region. The axons of spinothalamic cells cross immediately, in the same segment in which they are located (see Box 9-12), and enter the contralateral ventrolateral funiculus. Spinothalamic axons travel rostrally within the spinothalamic tract of the ventrolateral funiculus to reach the thalamus. *In sum, each ventrolateral funiculus contains information about pain and temperature from the contralateral side of the body.*

Finally, we consider the corticospinal pathway, which unlike the two sensory pathways, travels *down* the neuraxis from the cerebral cortex to the spinal cord. We pick up the pathway in the cervical spinal cord. Recall that the motor decussation is located at the spinomedullary junction, which means that within the spinal cord, the corticospinal pathway travels contralateral to its point of origin in the cerebral cortex and *ipsilateral to the muscles that it influences*. One point of clarification is necessary here. The corticospinal tract divides into two unequal parts at the motor decussation. A small portion, about 10%, of the axons from cortex, do not cross the midline and form the **anterior or ventral corticospinal tract** (vcst in Fig. 9-8C). The anterior corticospinal tract supports bilateral postural adjustments of the trunk and proximal limbs but is not involved in controlling fine movements with the hands or feet. For now, we focus on the majority of axons from motor cortex that cross at the motor decussation and descend in the **dorsolateral funiculus** as the **lateral corticospinal tract** (lcst in Fig. 9-8C). At the level of the targeted motoneurons, corticospinal axons leave the dorsolateral funiculus to enter the ipsilateral ventral horn, where they contact motoneurons and motor interneurons (Fig. 9-10C). The lateral corticospinal tract is primarily responsible for movements of the limbs and has little influence on trunk motoneurons in thoracic cord. *In sum, each dorsolateral funiculus contains axons critical to the voluntary movement of ipsilateral limb muscles.*

TEST YOUR UNDERSTANDING OF SPINAL CORD FUNCTION BY DEDUCING THE CLINICAL EFFECTS OF THREE LESIONS

Now is the time to realize how much clinically applicable information you have learned in this chapter. Consider the effect of three lesions on each of the three major pathways upon which we have focused: the dorsal column-medial lemniscus pathway, the spinothalamic pathway, and the corticospinal pathway.

First, we consider a spinal hemisection, a lesion that has been used effectively as a teaching tool for more than 150 years. Although a perfect hemisection rarely, if ever, happens, it is of such traditional importance that it has a name: the **Brown-Séquard syndrome** (Fig. 9-11A). So, what symptoms would we expect if half the spinal cord were cut?

Let us consider a left hemisection of the spinal cord, meaning that the spinal cord is cut completely from the midline to the left edge of the cord. There are three major consequences:

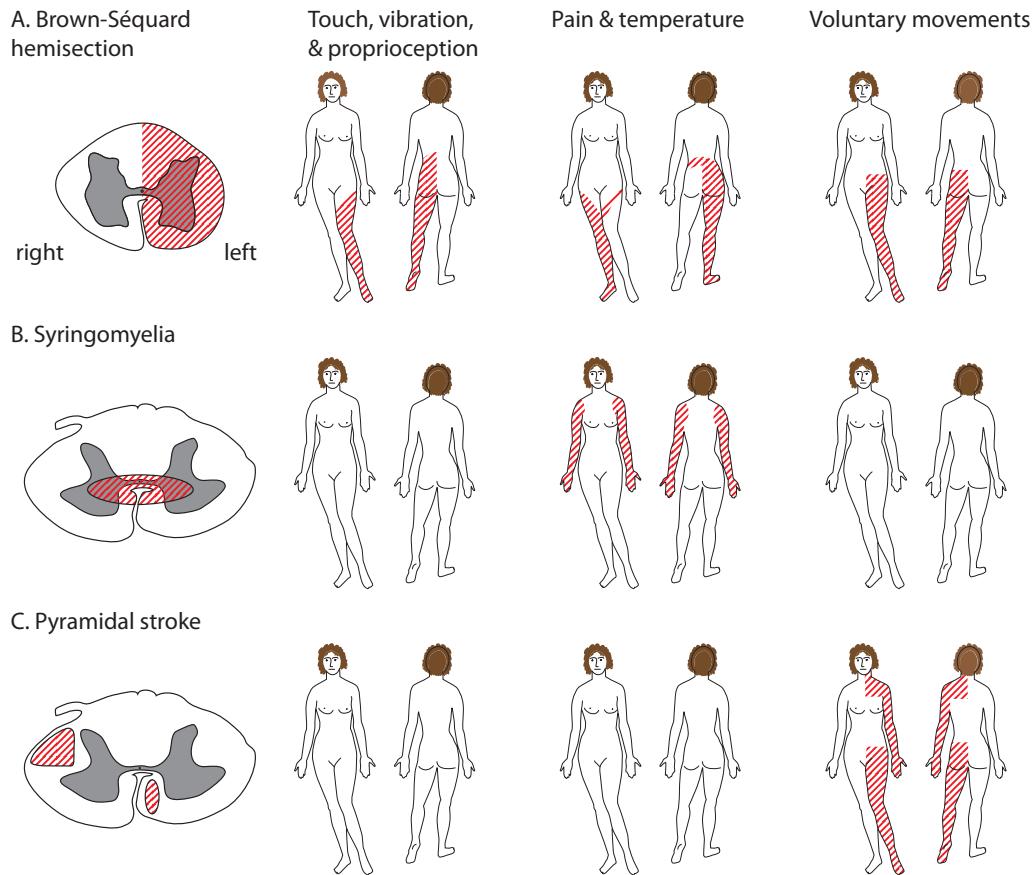


Figure 9-11. Three lesions that produce different constellations of symptoms are illustrated here. Note that sections are oriented according to radiological convention with the right side on the left and the left side on the right. **A:** A hemisection causes Brown-Séquard syndrome, which includes ipsilateral loss of tactile, vibratory, and proprioceptive sensation, contralateral loss of pain and temperature sensations, and ipsilateral loss of voluntary movements. In addition, pain and temperature sensations are lost bilaterally at the level of the hemisection. Illustrated here is the pattern of deficits after a left L2 hemisection. **B:** In its early stages, syringomyelia causes a lesion localized to the central canal region. This lesion affects only one of the three long pathways: the spinothalamic tract pathway. Axons crossing through the ventral spinal commissure are interrupted, causing a bilateral loss of pain and temperature sensations. Syringomyelia most commonly affects lower cervical segments; shown here are the deficits expected from a lesion affecting segments C6–C8. **C:** After a left pyramidal stroke, the axons in the right lateral corticospinal tract are no longer connected to the motor cortex. Therefore, voluntary movement of the right side will be severely impaired. The motor impairment due to unilateral, or one-sided, corticospinal tract damage is most severely apparent in limb movement. Voluntary movements of the trunk are far less impaired in part because the anterior corticospinal tract on the unaffected side can largely compensate. No sensory deficits are associated with damage to the corticospinal system.

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- Perception of all light touch, vibration, and proprioceptive stimuli arising from the same or ipsilateral side as the lesion, the left side, would be impaired for dermatomes at the level of and caudal to the lesion.
- Pain and temperature sensation would be impaired on the opposite or contralateral side, the right side, for dermatomes at the level of and caudal to the lesion. At the level of the lesion, pain and temperature would be impaired bilaterally.
- Voluntary movements would be impaired on the side ipsilateral to the lesion, the left side.

The above is accurate to a certain degree but omits a crucial detail. The deficits observed after a spinal hemisection will depend on the level of the lesion. A hemisection in the lumbar cord will result in impaired movement of and sensation from the leg, but the movement of and sensation from the arm will be unaffected. Thus, the above sensory and motor deficits stem from the interruption of long axonal tracts and therefore only apply to tissues innervated by segments at and caudal to the lesion.

Next, we consider a lesion affecting the central canal region (Fig. 9-11B), similar to the early effects of syringomyelia (see Box 9-12). First, a lesion of the central canal region has no effect on the voluntary movements as it does not reach the dorsolateral funiculus. Second, the dorsal columns are not affected, or minimally so. Consequently, a lesion in the central canal region produces no change in the sensations of touch, vibration, and proprioception. In contrast to the dorsal column-medial lemniscus and corticospinal pathways, the spinothalamic pathway is affected by syringomyelia. Recall that the axons of spinothalamic tract cells cross the midline just ventral to the central canal. These axons, which cross at the level of the primary afferent input, are lesioned. Therefore, pain and temperature sensations in the dermatome or dermatomes at the level of the lesion are impaired *bilaterally*.

Finally, we consider a stroke affecting the left pyramidal tract. Remember that the corticospinal tract travels in the medullary pyramids *above the motor decussation*. Therefore, a lesion of the left medullary pyramid would affect the right lateral corticospinal tract, which would impair voluntary movements of the right arm and right leg (Fig. 9-11C). Since the ventral corticospinal tract influences motoneurons innervating axial muscles *bilaterally*, voluntary movements of the trunk are far less impaired than are voluntary limb movements. Pyramidal lesions do not affect either the dorsal column-medial lemniscus or spinothalamic pathways, and consequently, no sensory symptoms are present.



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CHAPTER 10

CRANIAL NERVES: BRAIN SENTRYIES

The cranial nerves serve as sentries, well situated to provide the first indication of a serious problem and offer easily observed clues as to the location of a vascular or traumatic mishap. Yet, the functions of our cranial nerves are not part of our vernacular language. No one seeks medical help, saying, “Gee, the strangest thing happened last night; my right glossopharyngeal nerve went on the fritz,” or “I don’t understand it. My stylopharyngeus muscle is just not working right.” Therefore, although learning the names of the nerves and structures targeted by nerves aids in conversations with medical professionals, it does not facilitate effective communication with lay people including friends, family, and patients. To understand a patient’s concerns, we need to understand what cranial nerves do in *lay* terms. We need to translate a patient’s complaint into “cranial nerve-speak.” Therefore, in this chapter, we concentrate on how the cranial nerves support everyday life and on what goes wrong, in *everyday* terms, when they do not work correctly. Using this approach, the reader can understand the potential contributions of individual cranial nerves to complaints that a patient has difficulty swallowing, or that nothing “tastes” good, or that everything is blurry when trying to read. Armed with a solid knowledge of cranial nerve function and anatomy, the potential sources of many problems can be narrowed down. Further aided by a good history and neurological exam, you can make a best guess as to the nature and site of a lesion that will rival that made with the help of a radiological image.

Clearly, not all problems hinge on cranial nerve damage. Not even all symptoms involving cranial nerve-innervated structures result from cranial nerve damage. For example, damage to the facial muscles or their innervating nerve, the facial nerve, or damage to the corticobulbar tract within the central nervous system (CNS) can all cause difficulty in making facial expressions. How does one distinguish between a muscle problem, a nerve problem, and a brain problem? Essentially, by considering the *ensemble of symptoms* exhibited (Fig. 10-1). Each cranial nerve includes one or more components. A collection of symptoms that exactly reflects the particular components of one cranial nerve is astronomically more likely to result from damage to that cranial nerve than from damage to either the dispersed central nuclei or to the scattered peripheral targets involved. Further, most trauma, vascular accidents, and tumors are not so neat as to cleanly affect only one brain locus or one cranial nerve root. Therefore, knowing the location of cranial nerves with respect to other cranial nerves and underlying brain structures will allow you to accurately

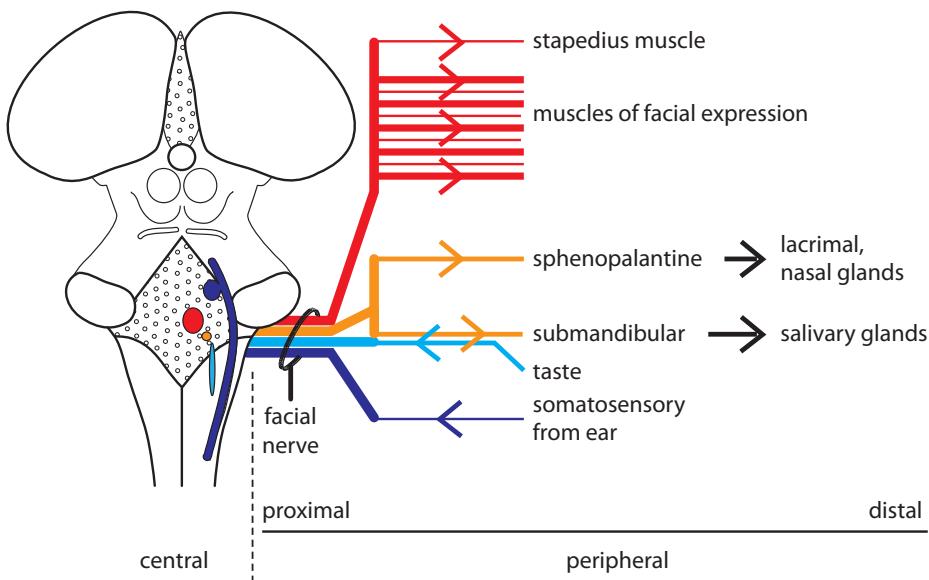


Figure 10-1. In the case of six cranial nerves (III, V, VII, VIII, IX, X), cells in multiple brainstem regions either send axons into or receive axons from a single cranial nerve. After exiting the skull, most of the cranial nerves split into smaller nerves that take divergent paths to reach peripheral targets. In the case of the facial nerve, illustrated here, four brainstem nuclei are connected to the nerve (more on this in Chapter 12). After exiting the skull, the facial nerve splits up into about a dozen smaller peripheral nerves to reach widespread target tissues. The major component of the facial nerve, motor output to the muscles of facial expression, is carried by five major nerves and a number of smaller nerves. Autonomic motor output to two parasympathetic ganglia is carried by two nerves, one of which also carries taste information back from the tongue into the brain. The facial nerve contains a small number of somatosensory afferents that innervate a region around the external auditory meatus of the ear. In sum, axons from several brainstem regions join together into the facial nerve and then diverge again to reach many distal targets. Consequently, injuries to the facial nerve pathway cause very different complements of symptoms, depending on the site of the lesion. A facial nerve lesion will impair all of the sensory, autonomic, and motor functions served by the facial nerve. Lesions that are progressively more distal, or far from the central nervous system, cause progressively more selective impairments of facial nerve function. Central lesions resemble distal lesions in that they often impair only one function of a cranial nerve. However, central lesions typically affect additional functions supported by areas neighboring the region involved in cranial nerve function.

guess the underlying cause of a problem, as well as to predict, and therefore look for, additional symptoms likely to accompany the presenting issue.

Cranial nerves differ from spinal nerves in that they exit from the skull or cranium rather than from the vertebral column. In addition, recall that spinal nerves are mixed, as they carry both sensory and motor axons, or fibers. In another contrast to spinal nerves, cranial nerve roots can contain only sensory fibers, only motor fibers, or a mixture of sensory and motor fibers. In this chapter, you will learn the target of each cranial nerve and, more importantly, the symptoms associated with dysfunction of each cranial nerve.

The cranial nerves are numbered with Roman numerals from I to XII, with I entering the olfactory bulb at the rostral tip of the brain and IX, X, and XII exiting from the caudal medulla. Each cranial nerve has a common name. The common names of all cranial nerves, the nature of their components, and the part of the brain from where the root exits (Fig. 10-2) are listed in Table 10-1.

Most cranial nerves serve one or a few related functions and are therefore fairly easy to learn and remember. The olfactory nerve carries olfactory information, the optic nerve carries visual information, and the vestibulocochlear nerve carries

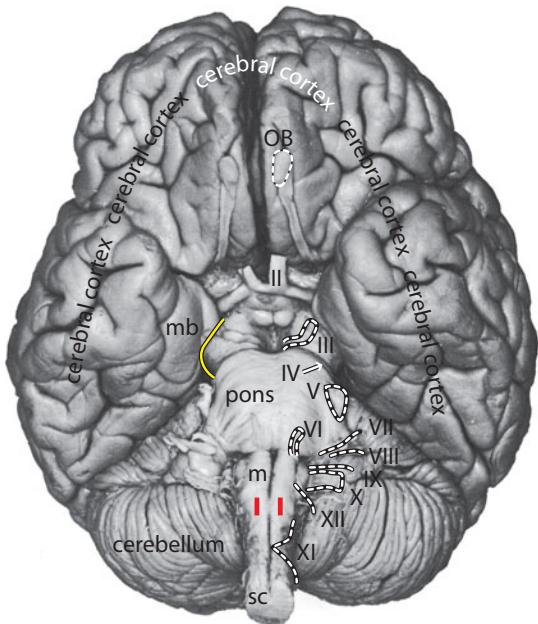


Figure 10-2. This photograph shows the brain from the ventral surface. The pyramidal decussation, located at the site flanked by two red lines, marks the junction between the spinal cord (*sc*) and medulla (*m*) and the location of the foramen magnum. Rostral to the medulla is the pons, which has a bulbous base. Rostral to the pons is the midbrain (*mb*), which is marked by the black and yellow line (see detail in Fig. 10-3). The roots of the cranial nerves are labeled on the right side of the photomicrograph. On the left side of the photograph, the roots of cranial nerves II, III, V, VI, VII, VIII, and X are visible. Cranial nerve I, the olfactory nerve, consists of a large number of tiny axons that connect the nasal epithelium to the olfactory bulb (*OB*). These tiny axons are not visible, but the bulb is clearly seen at the base of the frontal lobes. The root of cranial nerve IV exits from the dorsal side of the midbrain and snakes around to the ventral surface of the brainstem near the junction of the pons and midbrain (see arrow marked *IV*). However, it is very small and very difficult to see in this photomicrograph. The roots of cranial nerves IV and XI are also not visible on the left side of this photomicrograph.

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auditory and vestibular information from the inner ear. The abducens and trochlear nerves each innervate a single extraocular muscle capable of moving the eye in one direction. The spinal accessory and hypoglossal nerves carry motor output to muscles of the neck and tongue, respectively. The oculomotor nerve is more complex but nonetheless serves the related functions of eye movement, lens accommodation, and pupillary constriction.

The four cranial nerves with both sensory and motor components—V, VII, IX, X—are more challenging to learn and remember. Yet, three of the four have a dominant function. The trigeminal nerve carries the vast majority of the somatosensory input from the face and oral cavity. Along with this dominant role in facial sensation, the trigeminal nerve also carries motor output to muscles involved in chewing. The dominant role of the facial nerve is motor control of muscles involved in making facial expressions, and the primary function of the vagus nerve is parasympathetic output to the viscera above the hindgut. The glossopharyngeal nerve carries a hodge-podge of sensory, motor, and autonomic information with no single function dominating.

TABLE 10-1. CRANIAL NERVES ARE NUMBERED FROM ROSTRAL TO CAUDAL AND ROMAN NUMERALS ARE TRADITIONALLY USED

CRANIAL NERVE #	CRANIAL NERVE NAME	COMPONENTS	EXIT POINT
I	Olfactory	special sensory	forebrain
II	Optic	special sensory	forebrain
III	Oculomotor	somatic motor autonomic motor	midbrain
IV	Trochlear	somatic motor	midbrain
V	Trigeminal	somatosensory branchial motor	pons
VI	Abducens	somatic motor	pontomedullary junction
VII	Facial	branchial motor autonomic motor special sensory somatosensory	pontomedullary junction
VIII	Vestibulocochlear	special sensory	pontomedullary junction
IX	Glossopharyngeal	branchial motor autonomic motor special sensory viscerosensory somatosensory	medulla
X	Vagus	autonomic motor branchial motor special sensory viscerosensory somatosensory	medulla
XI	Spinal accessory	branchial motor	cervical spinal cord
XII	Hypoglossal	somatic motor	medulla

The number, common name, components, and exit point of the 12 cranial nerves are listed. The function of the *majority* of fibers in each nerve is in orange. Fibers of no single function comprise a majority of the glossopharyngeal nerve

ONLY A NEARLY COMPLETE, BILATERAL INJURY TO THE OLFACTORY NERVES WILL PRODUCE SYMPTOMS

The olfactory nerve consists of very thin, unmyelinated, short axons that arise from **olfactory sensory neurons** in the nasal epithelium and project into the **olfactory bulbs** at the very rostral tip of the brain. The delicate, thin axons of the olfactory nerve thread the skull's **cribriform plate**, where they are vulnerable to horizontal shearing action. The most common cause of olfactory nerve

damage is whiplash from a car accident. The quick back-and-forth movement shears the thin olfactory axons as they pass through the cribriform plate (see Table 10-2).

Anosmia or the inability to smell results only from injuries severe enough to sever all or most input to both bulbs. Yet, anosmic patients rarely present with the complaint that they cannot smell. Instead, they are more likely to complain that everything tastes bland; this follows from flavor's heavy dependence, estimated at about 80%, on smell more so than on taste (see Box 10-1). Since the nasal epithelium contains neural progenitor cells that continue to make new olfactory neurons throughout an individual's lifetime, one may surmise that anosmia due to whiplash would resolve once new olfactory sensory neurons are born. However, this typically is *not* the case, perhaps because scar tissue blocks the nascent sensory axons from entering into the olfactory bulb.

THE OPTIC “NERVE” CARRIES VISUAL INPUT FROM THE VISUAL FIELDS

The optic nerve is in fact not a nerve at all. Recall that the retina develops from the optic vesicle, itself an outpouching of the diencephalon (see Chapter 3). Therefore, the optic “nerve” is actually a tract, an axon bundle contained

TABLE 10-2. FOR EACH OF THE CRANIAL NERVES THAT SERVES A SPECIAL SENSE, THE SENSE SERVED, THE PERIPHERAL LOCATION OF THE NEURON CARRYING INFORMATION ABOUT THE SPECIAL SENSE, AND THE CENTRAL TARGET OF THE NEURON'S AXON ARE LISTED

CRANIAL NERVE	SENSE	LOCATION OF CELL BODY	AXONAL TARGET	SYMPTOM
Olfactory	Smell	Nasal epithelium	Olfactory bulb	Anosmia <i>only if lesion is bilateral</i> ; typically reported as a deficit in taste
Optic	Vision	Retina, ganglion cell layer	Lateral geniculate nucleus	Blindness
Facial	Taste on the anterior 2/3 of the tongue	Geniculate ganglion	Rostral portion of the nucleus tractus solitarius	Loss of taste on the ipsilateral tongue <i>upon examination</i>
VIII – vestibular component	Head position and motion	Scarpa's ganglion	Four vestibular nuclei	Disequilibrium, vertigo, nausea, oscillopsia, nystagmus and many others
VIII – cochlear component	Hearing	Spiral ganglion	Cochlear nuclei	Deafness or hearing loss
Glossopharyngeal	Taste on the posterior third of the tongue	Petrosal ganglion	Rostral portion of the nucleus tractus solitarius	Loss of taste on the posterior third of the tongue <i>upon examination</i>
Vagus	Taste on the uvula and epiglottis	Nodose ganglion	Rostral portion of the nucleus tractus solitarius	Loss of taste on the uvula and epiglottis <i>upon examination</i>

In addition, the most likely symptom to arise from damage is listed. This table and the next three tables are meant to be reference tables. The structures listed (e.g., the axonal targets listed in this table) that have not been introduced will be introduced in the next two chapters.

Box 10-1

FLAVOR DEPENDS ON MULTIPLE SENSORY MODALITIES.

Flavor is a *compound* sensation that integrates the primary senses of taste, smell, texture, and temperature. The largest contribution to flavor arises from smell. Even though taste plays a smaller role than smell in flavor, people commonly refer to a food's flavor as its "taste."

entirely within the CNS. Nonetheless, the term *optic nerve* is deeply entrenched in the medical and scientific vernacular as a term for the axons between the eye and the optic chiasm (Fig. 10-3) and will be used here with that meaning.

To understand the visual pathways, it is critical to first understand the concept of **visual fields**. Consider looking straight ahead. The point where you are looking is termed the point of **fixation**. This is the direction of your gaze. As you look straight ahead, the area to the right of your point of fixation is the right half of the visual field, and the area to the left of your point of fixation is the left half of your visual field (Fig. 10-4). Even if you turn your head to the right, the area to the left of your point of fixation remains your left visual **hemifield**, even if it is located on the right side of your body. In other words, the visual fields are named for their position *relative to your fixation point and not relative to your head or body*.

Each optic nerve carries information from the whole visual field of one eye, meaning the world visible to that eye (Fig. 10-5). We divide both the visual fields and the retinas into **temporal**, or outer and closer to the temple, and **nasal**, or inner and closer to the nose, halves. Light from a hemifield reaches the contralateral eye's temporal retina and the ipsilateral eye's nasal retina (see Box 10-2). In the case of the upper and lower hemifields, light reaches both eyes' inferior or superior retinas, respectively. For example, if you hold your right index finger out to the right at shoulder height while looking straight ahead, light bouncing off your finger will reach the temporal part of the left retina and the nasal part of the right retina. The image of your finger remains even if you close either eye because light from your finger reaches both retinas. The forward placement of our eyes allows both eyes to view most objects in the visual field. The part of the visual field that is viewable by both eyes is the **binocular** field. In total, more than 80% of the total human visual field strikes binocularly, upon both retinas.

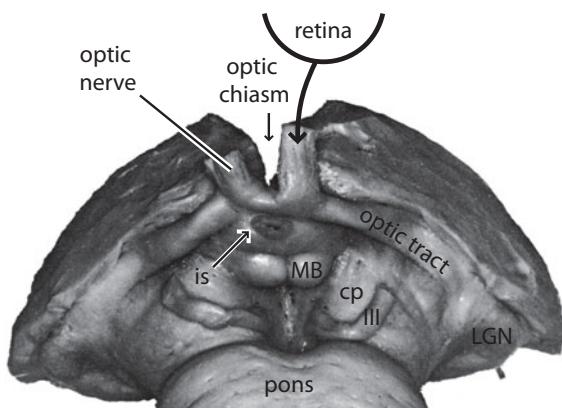
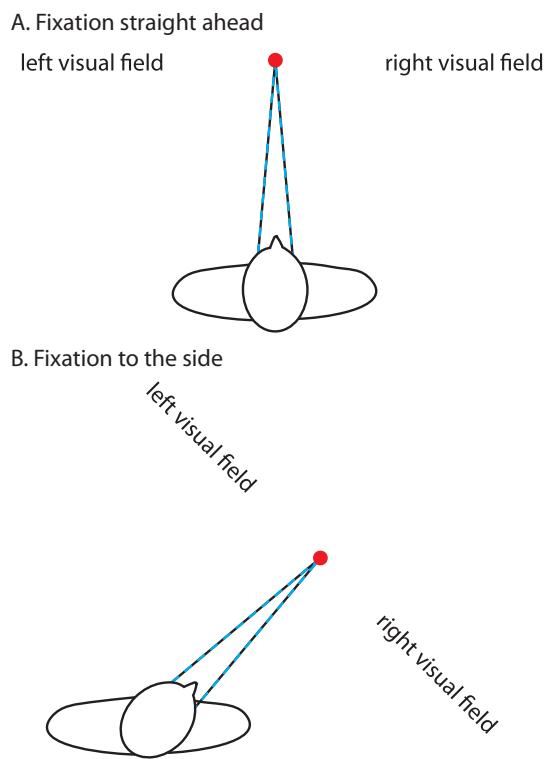


Figure 10-3. This photograph shows the ventral surface of the brain from the pons to the thalamus. Axons from retinal neurons travel through the optic nerve toward the optic chiasm. Some of the axons cross the optic chiasm to the contralateral optic tract and some retinal axons skirt the chiasm to travel in the ipsilateral optic tract (see Fig. 10-5). As the optic tract travels to the lateral geniculate nucleus (LGN) of the thalamus, it abuts the cerebral peduncles (cp), a major fiber tract at the base of the midbrain. Despite the different names, the optic nerve and the optic tract both contain the same retinal axons. Additional structures labeled for orientation include the pons, the oculomotor nerve (III), the infundibular stalk (is) and the mammillary bodies (MB).

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Figure 10-4. A: Everything to the right of the fixation point (red dot) is in the right visual field, and everything to the left is in the left visual field. The visual fields are always relative to the point of fixation rather than to the body axis. B: Thus, when a person fixates to the right, both the left and right visual fields are to the right of the body.



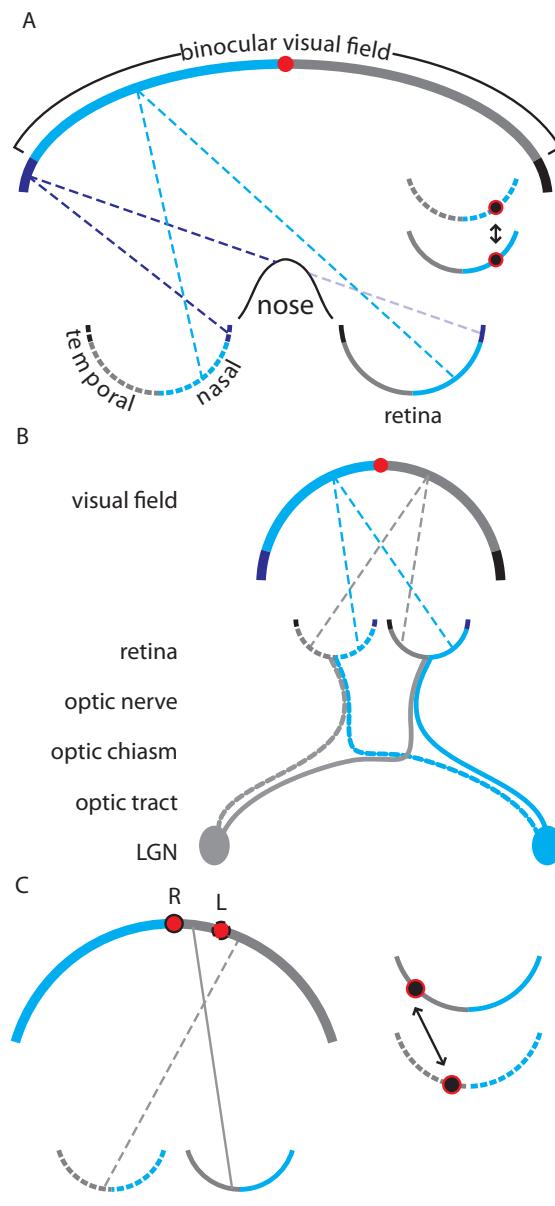
Now hold your finger out to the right side, at about 80 degrees, while fixating straight ahead. If you close your left eye, the image of your index finger remains and is unaltered, but if you close your right eye, the image of your index finger disappears (Fig. 10-5A). Your index finger is now in the monocular part of the visual field, the right monocular part specifically. Humans have about 150 degrees of binocular vision, flanked by 15 degrees or so of monocular vision on either side (see Box 10-3).

A PERSON WITH A SUDDEN HEADACHE, DOUBLE VISION, AND SENSITIVITY TO LIGHT SHOULD ELICIT SERIOUS CONCERN AND IMMEDIATE ACTION

The oculomotor nerve is a large nerve that exits from the base of the midbrain, just off midline (Figs. 10-2 and 10-3). As it exits from between the **cerebral peduncles**, which are two large white matter tracts at the base of the midbrain (see Fig. 3-10), the oculomotor nerve weaves precariously between two arteries, subject to pressure from either side (see Chapter 14).

As its name suggests, the oculomotor nerve is critical to moving the eyeball (Table 10-3). Six **extraocular muscles** attach onto the eyeball and move the eye in the horizontal, vertical, or **torsional** planes (Fig. 10-6). Horizontal eye movements move

Figure 10-5. A: The visual field covers almost 180 degrees, most of it binocular, centered at the fixation point (red dot). Each retina is divided in the horizontal axis between a nasal portion, closer to the nose, and a temporal portion, closer to the temple. Light (dashed lines) from the most peripheral 15 degrees or so of the visual field (dark blue) only reaches the ipsilateral nasal retina. It is blocked by the nose from reaching the contralateral temporal retina. This most peripheral portion of the visual field is the monocular portion. Light from the binocular portion of the left visual field (blue) hits the left nasal retina and the right temporal retina. The light hits both retinas at corresponding locations, located at the same eccentricity, or polar distance from the center (see inset). B: Visual pathways to the lateral geniculate nucleus (LGN) are illustrated. Light (dashed lines) from the right visual field (gray), the area right of the fixation point, hits the left (dashed lines) temporal retina and the right (solid lines) nasal retina. Light from the left visual field (blue), the area right of the fixation point, hits the right temporal retina and the corresponding point in the left nasal retina. Axons from the temporal retina project to the ipsilateral thalamus, whereas axons from the nasal retina cross in the optic chiasm to reach the contralateral thalamus. Because of the selective crossing of retinal axons, the right visual field is carried on the left side and the left visual field is carried on the right side beyond the optic chiasm. Therefore, retrochiasmic lesions, lesions caudal to the optic chiasm, produce contralateral visual field deficits. C: Diplopia results from the two eyes fixating on different sites. In the example illustrated, the left eye is fixated on a spot (L) to the right of where the right eye is fixated (R). As a result, two different spots in the visual field are represented in corresponding retinal locations (dashed lines). Conversely, as illustrated on the right, light from any one spot in the visual field hits noncorresponding spots on the retina.



the eye side to side, whereas vertical eye movements move the eye up and down. A horizontal movement of the eye toward the temple is called **abduction**, and one toward the nose is **adduction**. Up and down vertical eye movements are termed **elevations** and **depressions**, respectively. Torsional movements are rotations of the eyes around the axis going through the pupil. A rotation toward the nose is called **intorsion** and a rotation toward the temple is called **extorsion**.

The eyes *always* move together, in **conjugate**, during vertical and torsional movements. This means that if one eye moves up, the other eye also moves up. In the case of torsional movements, if one eye intorts the other eye extorts. A conjugate horizontal eye movement is when both eyes move to the right or both eyes move to the left. Note that conjugate horizontal eye movements require abduction of one eye and adduction of the other. In contrast to vertical and torsional eye movements, horizontal

Box 10-2

PEOPLE MAY MISATTRIBUTE A VISUAL FIELD IMPAIRMENT TO BLINDNESS IN ONE EYE.

Most people have never heard the term “visual field” nor do they understand its meaning. Therefore, people will often attribute right or left hemifield impairment to the right or left eye. For example, a person who does not see the right hemifield may complain of not being able to see out of the right eye. Each eye has a right and a left visual field. An assessment of a patient’s vision fields is always done on one eye at a time. The patient is asked to look with one eye and to shut the other eye. However, anatomical lesions of the retina or optic nerve do not produce **homonymous** visual field deficits, meaning deficits that affect the same part of the

visual field in both eyes. For example, a lesion of the right optic nerve would cause a loss of vision in the right and left hemifields of the right eye. Vision of the left and right hemifields is preserved in the left eye in this example. In contrast, retrochiasmal lesions, meaning lesions that are caudal to the optic chiasm (Fig. 10-5B), uniformly cause homonymous visual field deficits. An example of a homonymous visual field deficit is the effect of a lesion of the optic tract on the left side. Such a lesion will result in the inability to see the right visual field *from either eye*. This symptom is termed a right **hemianopia**, meaning “blindness” to the right visual field.

Box 10-3

DAMAGE TO AN EYE OR TO AN OPTIC NERVE CAUSES BLINDNESS IN THAT EYE.

Either retinal damage or damage to the optic nerve can cause blindness. Retinal damage can result from a number of conditions such as **glaucoma** or **macular degeneration**, as well as from trauma. Optic nerve damage is rarer with the most frequent cause being **optic neuritis**, an inflammation of the nerve often found in patients who either have or develop **multiple sclerosis**.

eye movements can either be in conjugate, for example during a sideways glance, or **disconjugate** when focusing on a near object. The only healthy disconjugate movements are **vergence**, when both eyes adduct in toward the nose, and the relaxation from vergence when both eyes return from an adducted position.

There are six extraocular muscles. Four of these muscles are **rectus** muscles, and they insert on the anterior half of the globe (Fig. 10-7). When a rectus muscle contracts, the pupil rotates toward the back of the eye. For example, the **superior rectus** attaches to the top of the globe and consequently contraction of the superior rectus pulls the top of the globe backward, so that the eye rotates upward. In contrast, two of the extraocular muscles are **oblique** muscles that attach to the posterior half of the globe. This reverses the direction of eye movement. For example, the **superior oblique** attaches to the top of the eye but, unlike the superior rectus, it attaches to the back of the eye. Thus, when the superior oblique contracts, it pulls the top of the eye forward, which rotates the direction of gaze downward.

The oculomotor nerve innervates four of the six extraocular muscles that move the globe:

- **Medial rectus** adducts the eye toward the nose.
- Superior rectus elevates the eye upward.
- **Inferior rectus** depresses the eye downward.
- **Inferior oblique** has multiple actions, including elevation and extorsion.

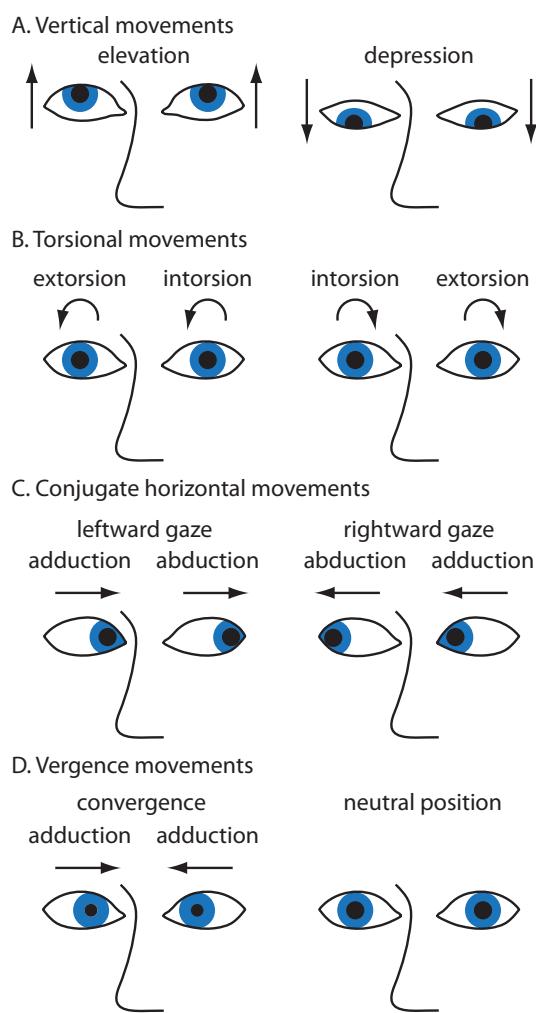
Because both muscles capable of elevating the eye, the superior rectus and the inferior oblique, are innervated by the oculomotor nerve, an injury to this nerve will result in the inability to look up. The oculomotor nerve innervates a fifth skeletal muscle but one that is not an extraocular muscle since it does not attach to the eye. The **levator palpebrae** muscle supports voluntary eyelid elevation.

TABLE 10-3. FOR EACH OF THE CRANIAL NERVES THAT INNERVATES SKELETAL MUSCLE, THE TYPE OF MUSCLE, CENTRAL LOCATION OF THE MOTONEURON, AND MUSCLES INNERVATED ARE LISTED

CRANIAL NERVE	BRANCHIAL OR SOMATIC	LOCATION OF CELL BODY	MUSCLES INNERVATED	MUSCLE ACTION	IMPAIRMENT
Oculomotor (III)	Somatic	Oculomotor nucleus	Medial rectus Contralateral superior rectus Inferior rectus Inferior oblique Levator palpebrae	Adduction Elevation / intorsion Depression / extorsion Extorsion/ elevation Eyelid elevation	Lateral gaze, vergence Vertical gaze, torsion Vertical gaze, torsion Vertical gaze, torsion Ptosis
Trochlear (IV)	Somatic	Trochlear nucleus	Contralateral superior oblique	Intorsion / depression	Vertical gaze, torsion
Trigeminal (V)	Branchial	Trigeminal motor nucleus	Muscles of mastication Tensor tympani	Chewing Tightens tympanic membrane	Hyperacusis
Abducens (VI)	Somatic	Abducens nucleus	Lateral rectus	Abduction during lateral gaze	Lateral gaze
Facial (VII)	Branchial	Facial motor nucleus	Muscles of facial expression Stapedius Stylopharyngeus	Ability to make facial expressions Pulls stapes off oval window Elevates palate	Bell's palsy Hyperacusis Dysphagia, dysarthria, loss of gag reflex
Vagus (X)	Branchial	Nucleus ambiguus	Muscles of pharynx, larynx, and soft palate (except stylopharyngeus)	Gagging, speech, swallowing	Hoarseness, breathy speech, dysphagia
Spinal accessory (XI)	Branchial	Accessory nucleus	Sternocleidomastoid Trapezius	Turns head contralaterally Shoulder shrug	Deficit in turning head Deficit in shrugging
Hypoglossal (XII)	Somatic	Hypoglossal nucleus	Glossus (tongue) muscles	Moves tongue	Tongue deviates ipsilaterally upon protrusion

The muscles innervated are always ipsilateral except in the two cases marked contralateral. In addition, the movement produced by each muscle and/or the symptom produced by damage is listed. For each extraocular muscle, the primary and secondary muscle actions are listed. This table is intended as a reference. The reader will learn the nuclei listed under "location of cell body" in the next two chapters

Figure 10-6. There are three axes about which the eyes move—vertical, torsional, and horizontal. Vertical (A) and torsional (B) movements are always conjugate, meaning that the two eyes move together in the same direction. Horizontal movements can either be conjugate (C) or disconjugate, in the case of vergence movements (D). **A:** Moving the eyes up and down is termed elevation and depression. **B:** Rotating the eyes around the axis going through the pupil is called torsion, with rotating the eyes toward the nose termed intorsion and away from the nose, extorsion. **C:** Moving an eye in the horizontal plane toward the nose is termed adduction, and moving it toward the temple is abduction. **D:** When viewing near objects, the two eyes converge. This convergence is disconjugate with both eyes adducting. In addition, the pupil narrows during near viewing. For viewing far objects straight ahead, the eyes adopt the neutral position.



The oculomotor nerve contains preganglionic parasympathetic neurons that control the **ciliary** and **pupillary constrictor** muscles (smooth muscles) involved in **accommodation**, adjustments that allow for the focus of close objects upon the retina, termed **near vision** (see Box 10-4 and Table 10-4). Impairment of the oculomotor nerve therefore will lead to any, some, or all of the following symptoms:

- Double vision or **diplopia**: When the innervation of one or more of the extraocular muscles is interrupted, the two eyes will no longer view the same point in space (Fig. 10-5C). This will cause one area of visual space to be focused on the retina of one eye and a different area of visual space to be focused on the corresponding part of the retina of the other eye. Even if those locations are out of register by only a small distance, different scenes will fall on the eyes, producing what we commonly refer to as double vision. An easy way to determine whether double vision results from mispositioning of the

Figure 10-7. A: The eye approximates a globe in shape and sits within the bony orbit. Therefore, we can consider the circumference halfway between the cornea in the front and the optic nerve in the back as the equator. Four of the extraocular muscles attach to the globe at a point anterior to the equator. These four muscles—medial, lateral, inferior, and superior recti—all pull the eye back (red arrow in B), so that the pupil rotates toward the muscle. In contrast, the remaining extraocular muscles, the inferior and superior oblique muscles attach to the globe posterior to the equator. When the oblique muscles contract, the eye rotates toward the front (blue arrow in B). C: The lateral and medial recti (*lr*, *mr*) pull the eye laterally and medially, respectively. D: The superior rectus elevates the eye from the neutral position. The inferior rectus depresses the eye in an analogous fashion (not shown). E: The superior oblique pulls the eye toward the nose, a movement that is termed intorsion, when the eye starts in the neutral position (see Fig. 10-6D). F: The pulling directions of the extraocular muscles change according to the initial position of the eye in the orbit. For example, when the eye is adducted, the action of the superior oblique is primarily to depress the eye.

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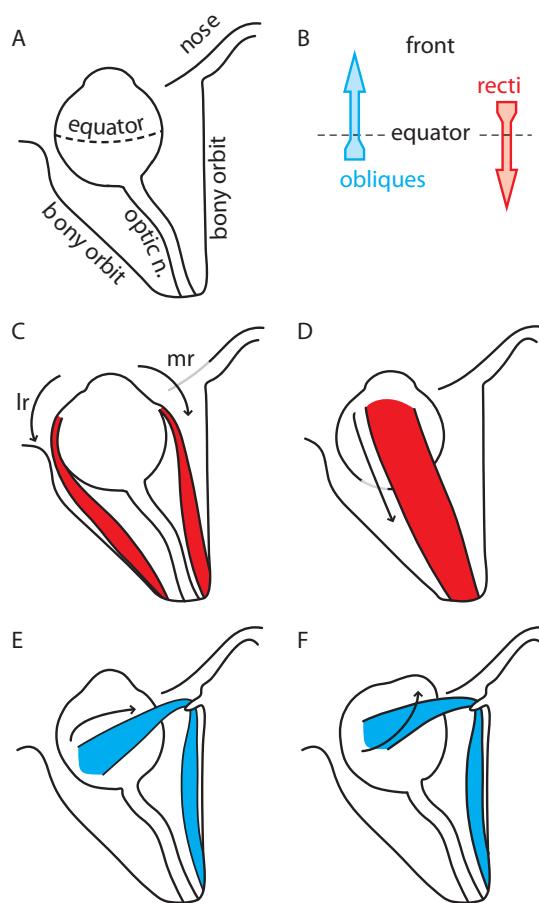


TABLE 10-4. FOUR CRANIAL NERVES COMprise THE CRANIAL PORTION OF THE PARASYMPATHETIC SYSTEM

CRANIAL NERVE	LOCATION OF PREGANGLIONIC NEURON	GANGLION	AREA/TISSUES INNERVATED	EFFECT	IMPAIRMENT
Oculomotor (III)	Edinger-Westphal nucleus	Ciliary	Ciliary muscle (lens) Pupillary constrictor muscle	Accommodation	Presbyopia Mydriasis
Facial (VII)	Superior salivatory nucleus	Pterygopalatine	Lacrimal gland	Tear production, nasal secretions	Dry eyes, dry nose
		Submandibular	Submandibular and sublingual glands	Salivation	Dry mouth
Glossopharyngeal (IX)	Inferior salivatory nucleus	Otic	Parotid gland	Salivation	Dry mouth
Vagus (X)	Dorsal motor nucleus of the vagus	Parasympathetic ganglia in the innervated tissues	Trachea, lungs, larynx, heart, digestive tract from esophagus through midgut, pancreas, and other thoracic and abdominal viscera	Promote recuperation and digestion, lower heart rate, and many others	No dramatic symptoms after unilateral lesion

For each nerve, the central location of the preganglionic neuron, the identity of the parasympathetic ganglion, the tissue innervated, effect of stimulation and impaired functions are listed. This table is intended as a reference. The reader will learn the nuclei listed under “location of preganglionic neuron” in the next two chapters.

Box 10-4

THE NEAR TRIAD ALLOWS CLOSE OBJECTS TO BE FOCUSED UPON THE RETINA.

The oculomotor nerves execute the **near triad**, a collection of three adjustments that allow one to fixate on something up close. You can see two of the three reactions by watching someone as they switch their gaze from the horizon to a finger held in front of their face. Most obviously, you will see that the two eyes **converge**, a necessary movement to align both eyes to fixate upon something close. Also observable, but more difficult to see, is that the pupil will contract. A small pupil, like a pinhole lens in a camera, greatly increases the depth of field, so that not only one central point but points in back and in front are all in focus (see Fig. 16-8). The third component of the near triad is a parasympathetically mediated rounding of the lens. Changing the shape of the lens changes the angle at which light hits the lens and therefore the depth to which light is focused by the lens (see more in Chapter 16). Unfortunately, the lens grows stiffer with age, so that this final component of the near triad fails noticeably in people during their fifth decade, producing **presbyopia**, or the inability to focus on near objects. Presbyopia is the reason for the pervasive need for “reading glasses” among people over 40 to 45 years of age.

eyes, as is typical, or from a problem with the visual system is to simply close one eye. If the problem goes away, eye movements are to blame, and if the problem persists, the visual system is to blame.

- **Droopy eyelids or ptosis:** Interruption of the levator palpebrae innervation results in droopy eyelids. However, in the absence of levator palpebrae contraction, the eyelids do not close completely during waking because the superior tarsal muscle, a smooth muscle innervated by the sympathetic nervous system, remains active and the superior tarsal muscle attaches to the levator palpebrae (see Box 9-3). The superior tarsal muscle is controlled by the sympathetic system, so that the eyes are open during waking and increasingly open during periods of arousal.
- **Oscillopsia** is a form of visual inconstancy in which images are perceived as moving or oscillating. To understand what this looks like, twirl yourself around a few times and then stop. Your eyes will beat back and forth in a pattern called **optokinetic nystagmus**. This oscillation is perfectly healthy and is discussed further in Chapter 26. To return to the subject at hand, the visual image that you have immediately after twirling yourself around is in fact oscillopsia. Oscillopsia can result from third-nerve damage but also occurs after lesions of a diverse number of other structures as described in Chapter 26.
- Large or “blown” pupil, termed **mydriasis**: Preganglionic parasympathetic innervation of the **ciliary ganglion** travels in the oculomotor nerve. Parasympathetic neurons in the ciliary ganglion innervate the pupillary sphincter muscle. Interruption of the parasympathetic input to the pupillary constrictor results in the reduction or absence of any constriction to oppose the tonic pupillary dilation driven by sympathetic activity. Mydriasis can in turn produce **photophobia** or sensitivity to light.
- **Presbyopia** or the inability to accommodate or see near objects: The oculomotor nerve innervates cells of the ciliary ganglion that provide parasympathetic innervation to the **ciliary** muscle of the lens. Activation of the ciliary muscle makes the lens more spherical, with a shorter focal length. Therefore, an interruption of the parasympathetic input to the ciliary muscle will result in the inability to focus on near objects. Trying but failing to do so will cause eyestrain and headaches.

Oculomotor nerve axons that innervate skeletal muscles arise from a different brainstem region than the preganglionic parasympathetic axons that innervate the ciliary ganglion. Therefore, *a single lesion that impairs both skeletomotor and parasympathetic oculomotor functions is far more likely to arise from an injury to the oculomotor nerve than to the brain*. Acute signs of oculomotor nerve impairment, such as a blown pupil, often result from a dangerous increase in intracranial pressure (see Chapter 14). When associated with a sudden-onset headache or any degree of unresponsiveness, oculomotor symptoms should be interpreted as a sign of a cerebrovascular accident and treated as an emergency.

THE TROCHLEAR NERVE IS AN EXCEPTIONAL CRANIAL NERVE

The trochlear nerve arises from the dorsal surface of the midbrain, crosses the midline, and wends its way around to the ventral side of the brainstem (Fig. 10-8). It is the only cranial nerve to exit from the dorsal surface of the brainstem, and the only one to cross the midline. The trochlear nerve is small as it innervates only one muscle, the superior oblique (Table 10-3), an extraocular muscle that depresses and intorts the eye (Fig. 10-7E, F). Because the superior oblique's action is most apparent only when the eye is in certain positions, trochlear nerve palsy may not be readily detected by either the patient or an examiner.

THE TRIGEMINAL NERVE CARRIES SOMATOSENSORY INFORMATION FROM THE FACE AND ORAL CAVITY

The large trigeminal nerve exits from the lateral edge of the pontine base, the basis pontis (Fig. 10-2). The largest of the cranial nerves, the trigeminal nerve has two components, a large sensory one and a modest motor one. Sensory-wise, the trigeminal nerve comprises fibers from cells in the **trigeminal ganglion**, also known as the **Gasserian** or **semilunar** ganglion, that carry somatosensory information—touch, vibration, pressure, pain, temperature, proprioception—from the face and oral cavity (Table 10-5). The trigeminal ganglion is essentially the face's version of a dorsal root ganglion as it contains virtually all of the primary somatosensory neurons that innervate the face and oral cavity.

A smaller component of the trigeminal nerve, which actually exits discernibly separately from the larger sensory root, carries motor axons that control muscles of mastication such as the masseter and digastric muscles that close and open the jaw, respectively (Table 10-3). The trigeminal nerve also controls the **tensor tympani**,

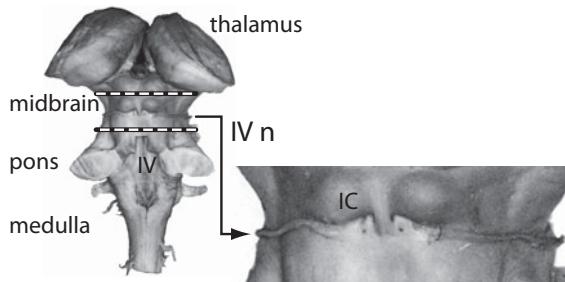


Figure 10-8. The trochlear nerve (IV n) exits from the dorsal surface of the brainstem, the only cranial nerve to do so. A dorsal view of the brainstem, with the cerebellum removed is shown with the medulla, pons, midbrain, thalamus, and fourth ventricle (IV) labeled for orientation. A magnified view of the region between the dashed lines, shown at right, shows the exit point of the trochlear nerve, near the junction between the pons and midbrain and just caudal to the inferior colliculi (IC).

Photograph reprinted with permission from deArmond S., et al. *Structure of the human brain: A photographic atlas*. New York: Oxford University Press, 1989.

a muscle in the middle ear that adjusts the tension of the **tympanic membrane**. In response to loud sounds, contracting the tensor tympani decreases sound sensitivity (see Chapter 17). Unlike most skeletal muscles, the tensor tympani contracts *automatically*, in response to loud sounds, and cannot be willfully controlled (see Box 10-5). Loss of tensor tympani function results in **hyperacusis**, auditory hypersensitivity, such that everything sounds uncomfortably loud.

The trigeminal dermatome is larger and more complex than the typical spinal dermatome. The trigeminal nerve splits into three bundles as it leaves the trigeminal ganglion. These three bundles form the **ophthalmic**, **maxillary**, and **mandibular** branches of the trigeminal nerve, carrying information from eponymous regions of the face (Fig. 10-9). The trigeminal nerve does not carry sensory input from a region of skin around the ear, the outer ear canal, the pharynx, and the back of the tongue, regions innervated by other cranial nerves. It is also important to remember that cervical spinal nerves, rather than the trigeminal nerve, innervate the back of the head, most of the back side of the ear, and the skin of the neck.

TABLE 10-5. THERE ARE ONLY FOUR CRANIAL NERVES THAT SERVE A VISCEROSENSORY OR SOMATOSENSORY FUNCTION

CRANIAL NERVE	VISCERAL OR SOMATIC	LOCATION OF CELL BODY	AREA/TISSUES INNERVATED	TARGET NUCLEUS	IMPAIRMENT
Trigeminal (V)	Somatic	Trigeminal ganglion	Face, teeth, tongue, most of oral cavity, meninges, cornea, nasal sinuses	Spinal trigeminal nucleus, main sensory nucleus	Anesthesia, dysesthesia, pain
Facial (VII)	Somatic	Geniculate ganglion	Region immediately around the ear canal	Spinal trigeminal nucleus, main sensory nucleus	Anesthesia, dysesthesia, pain
Glossopharyngeal (IX)	Somatic	Jugular ganglion	Back of external ear, middle ear, inner surface of the tympanic membrane	Spinal trigeminal nucleus, main sensory nucleus	Anesthesia, dysesthesia, pain
	Visceral	Petrosal ganglion	Pharynx, posterior third of tongue, carotid body (chemosensory), carotid sinus (blood pressure)	Nucleus tractus solitarius	Gag reflex
Vagus (X)	Somatic	Jugular ganglion	Pharynx, ear canal, outer surface of the tympanic membrane, meninges of the posterior fossa, small region of the ear	Spinal trigeminal nucleus	Anesthesia, dysesthesia, pain
	Visceral	Nodose ganglion	Trachea, esophagus, epiglottis, lungs, heart, aortic arch and other thoracic and abdominal viscera	Nucleus tractus solitarius	Cough reflex

For each of the four, the type of sensory function, location of the primary afferent, tissues innervated, target nucleus, and impairment are listed. This table is intended as a reference. The reader will learn the nuclei listed under “target nucleus” in the next two chapters.

Box 10-5

REFLEXIVE SOUND DAMPENING CAN OCCUR IN ANTICIPATION OF CHEWING.

The tensor tympani may contract during chewing or even *in anticipation of chewing*, to dampen sounds from the mouth conducted through bone. Like the contraction in response to loud sounds, the contraction of the tensor tympani in anticipation of chewing, or even speech production, is an automatic reaction and not under voluntary control.

The face and oral cavity have an unusual number of special structures by which humans sense exquisite pain but little other somatic sensation such as vibration, coolness, or warmth. These pain-producing structures are innervated by the trigeminal nerve and include the meninges covering the forebrain, the nasal sinuses, cornea, and teeth (see Box 10-6).

Unlike motor nerve lesions, *impairment of sensory nerves, including the trigeminal nerve, produces positive signs far more frequently than negative signs* (see Box 1-1). In other words, a motor nerve lesion produces an absence of movement, but a sensory nerve lesion typically produces *abnormal* sensation, or dyesthesia, rather than an absence of any sensation. A common abnormal sensation is “pins and needles,” such as one feels after unbending a limb that has “fallen asleep.” Far less common and far more distressing, sensory nerve lesions can initiate painful dysesthesias (see Box 10-7), such as **trigeminal neuralgia** or **burning mouth syndrome**.

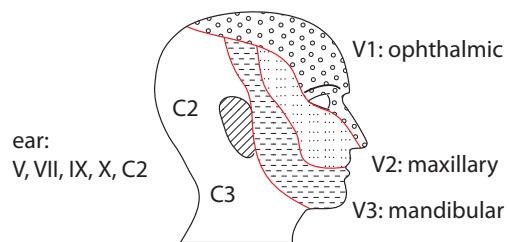
THE ABDUCENS NERVE SERVES LATERAL GAZE

Abducens roots straddle the basilar artery as they exit from the pontomedullary junction near the midline. Like the trochlear nerve, the abducens nerve innervates a single extraocular muscle, in this case the **lateral rectus** (Fig. 10-7C; Table 10-3). However, the lateral rectus, which **abducts** the eye, is a larger muscle than the superior oblique, and consequently, the abducens nerve is larger than the trochlear nerve. Like oculomotor and trochlear nerve palsies, abducens nerve palsy produces diplopia, but only when looking to the side of the affected nerve. There are a number of reasons that lead to abducens nerve dysfunction including tumors, aneurysms, and even sinus infections.

FACIAL EXPRESSION DEPENDS ENTIRELY ON THE FACIAL NERVE

Facial nerve exits from the lateral edge of the pontomedullary junction and weaves through the internal auditory meatus, passing through a bony canal in the inner ear to reach the face. The primary function of the facial nerve is controlling the muscles of facial expression (Table 10-3). The facial nerve allows us to smile, frown, squint, and wink (see Box 10-8). When the facial nerve is inoperative,

Figure 10-9. Fibers exit the trigeminal ganglion in three bundles, or branches, destined for three different regions of the face. Each region of the face is innervated by one branch of the trigeminal nerve. The *external regions* supplied by the ophthalmic (also termed V₁), maxillary (V₂), and mandibular (V₃) branches of the trigeminal nerve are shown. Unlike the case with spinal dermatomes, there is little overlap between the regions supplied by the three branches of the trigeminal nerve. The skin of the ear is innervated by spinal nerve C₂ and cranial nerves V, VII, IX, and X. The back of the head and neck is innervated by spinal nerves C₂ and C₃.



Box 10-6

HEADACHE PAIN IS ACTUALLY DURAL PAIN REFERRED TO MORE SUPERFICIAL TISSUES.

Headache is an example of **referred pain** (see Chapter 18). Intracranial inflammation or damage is sensed by dural afferents traveling in the trigeminal and high cervical nerves; the trigeminal nerve innervates the meninges of most of the forebrain, and cervical dorsal roots innervate the dura covering the brainstem. Trigeminal afferents from dura and skin converge onto the same central sensory neurons, which consequently “cannot tell the difference” between the two inputs. Activity in dural afferents is interpreted as activity in cutaneous afferents, often from the ophthalmic division. Thus, a **headache** is in fact a “duralache.” Many effective headache treatments are designed to block the initial excitation by inflammatory chemicals of trigeminal afferents that innervate the dura.

the mouth droops and the forehead smoothes out, demonstrating the contribution of the facial nerve to our appearance, even to our wrinkles and even at so-called rest (Fig. 10-10).

The facial nerve innervates the **stapedius**, a muscle which, like the tensor tympani, modifies middle ear sound transmission. In response to loud sounds, the stapedius contracts, thereby decreasing sensitivity to future sounds. Without the stapedius reflex, loud sounds arrive to the inner ear at full volume, resulting in great discomfort; recall that this symptom is termed **hyperacusis**.

The facial nerve contains the preganglionic parasympathetic innervation for tear production, nasal secretions, and salivation (see Box 10-9 and Table 10-4). Facial nerve axons target parasympathetic neurons in the **pterygopalatine**, also known as the **sphenopalatine, ganglion** that controls tear production in the **lacrimal gland** and nasal secretions from the nasal mucosa, for crying and nasal lubrication, respectively (Fig. 10-1). Facial nerve regulation of salivation derives from parasympathetic neurons in the **submandibular ganglion** that control secretions of saliva from the **submandibular** and **sublingual glands**. Because of the parasympathetic components of the facial nerve, *facial nerve dysfunction can cause dryness of the eyes, mouth, and nose*. The facial nerve receives special sensory information from sensory neurons in the **geniculate ganglion** that innervate **taste buds** located in the front two-thirds of the tongue. Finally, the facial nerve carries somatosensory information from a small region around the opening of the ear (Table 10-5).

In sum, dysfunction of the facial nerve leads to the following symptoms:

- Loss of facial expression on one side
- Hyperacusis
- Dry eye
- Dry mouth
- Pain around the ear canal: Remember that dysfunction of sensory nerves typically gives rise to a dysesthesia rather than to anesthesia.

Box 10-7

TRIGEMINAL PAIN SYNDROMES CAN CAUSE EXCRUCIATING, INTOLERABLE PAIN.

Recall from Chapter 1 that damage to sensory pathways often causes *positive* rather than negative signs. Sensory dysesthesias are sensations that occur in response to an inappropriate stimulus. For example, pain that is elicited by touch and numbness that occurs spontaneously are both inappropriate sensations for the situation. The trigeminal nerve is host to two notable painful dysesthesias: trigeminal neuralgia and burning mouth syndrome. Patients with

trigeminal neuralgia or **tic douloureux** feel electric and excruciating pain that shoots down the face, typically down the jaw. The jolts of pain can be triggered by the lightest touch or even occur spontaneously. Trigeminal neuralgia is difficult to treat and, when ineffectively managed, can drive its sufferers to suicide. Less common and less understood is burning mouth syndrome which, as its name suggests, involves a sensation that one's mouth is ablaze.

- Some compromise in taste: This is unlikely to rise to the level of a complaint in many people as taste buds on the palate and back third of the tongue are unaffected, as would be all the taste buds on the side contralateral to a nerve lesion. Further, as mentioned above, smell dominates taste in determining flavor, which is what people experience when eating.

Due to the multiple functions provided by the facial nerve, impairment of the facial nerve can result in a mixture of symptoms (see Box 10-10).

HEARING AND BALANCE DEPEND ON THE VESTIBULOCOCHLEAR NERVE

The vestibulocochlear nerve exits the brainstem at the **cerebellopontine angle** just lateral to the facial nerve (Fig. 10-11). It has two components: one for hearing and one for sensing the head's orientation and movement in space (Table 10-2). The cochlear nerve contains fibers from the **spiral ganglion** that innervate the **cochlea**, our auditory sensor. Impairment of a cochlear nerve causes hearing loss in the ear on the same side. Since hearing loss is easier to treat when it is mild, and since many causes of hearing loss are progressive, the cause of a notable hearing loss should be aggressively pursued.

The vestibular nerve contains fibers from **Scarpa's ganglion** that innervate the **vestibular apparatus**. One of the most common tumors affecting the nervous system

Box 10-8

THREE CONTROL MECHANISMS REGULATE EYE OPENING AND CLOSING.

Three muscles share the responsibility of covering or unveiling the eye: the levator palpebrae innervated by cranial nerve III, the orbicularis oculi innervated by cranial nerve VII, and the superior tarsus innervated by sympathetic nerves. The levator palpebrae and superior tarsus are both muscles of the eyelid, whereas the orbicularis oculi is a muscle that encircles the eye. The levator palpebrae and orbicularis oculi are skeletal muscles under voluntary control, and the superior tarsus is a smooth muscle under the automatic control of the sympathetic nervous system.

Contraction of the levator palpebrae or superior tarsus opens the eyes by lifting the eyelid, whereas contraction of the orbicularis oculi muscles covers the eyes by pulling the skin around the eyes toward the pupil. During eye movements, the contraction

and relaxation of the levator palpebrae control the elevation and depression of the eyelids. During elevation and depression of the eye, the role of the levator palpebrae in lifting and lowering the eyelids is particularly important and noticeable (Fig. 10-6A). Contraction of the orbicularis oculi pushes the eyelid as well as facial skin toward the pupil and over the eye. Blinking and winking are accomplished by a combination of levator palpebrae and orbicularis oculi actions. The superior tarsus acts, like the levator palpebrae, to lift the eyelid but is not under voluntary control. Thus, it is the sympathetically innervated superior tarsus that keeps the eyelids open during wakefulness and allows them to close during sleep. When sympathetic nerve activity decreases, the superior tarsus relaxes, producing a tell-tale sign of drowsiness.



Figure 10-10. A person with Bell's palsy cannot contract muscles on the affected side of the face. All facial expressions, even wrinkles, depend on activity in the facial nerve. Therefore, patients have far fewer wrinkles on the affected half of the face than on the unaffected half. Particularly notable are the absences of a **nasolabial fold** (arrow), the wrinkle between the lateral edges of the nose and mouth, and forehead wrinkles (in older patients) on the affected side. A young woman with a left sided Bell's palsy (A) and a young man with a right sided Bell's palsy (B) are shown as they attempt to smile, demonstrating the asymmetric smile of patients with Bell's palsy.

Modified from Harrison, D.H. Surgical correction of unilateral and bilateral facial palsy. *Postgrad Med J* 81:562–567, 2005, with permission of the publisher, BMJ Publishing Group Ltd.

is an acoustic neuroma, which, despite its name, usually stems from an overproduction of Schwann cells in the vestibular nerve (see Box 10-11). The vestibular apparatus contains patches of sensory epithelium sensitive to angular or linear head acceleration, including the accelerating force of gravity. A person with a lesion of the vestibular nerve may feel a sense of **vertigo**, **disequilibrium** or **dizziness**. Vertigo refers to a sense of rotatory motion, so that to an affected individual, either the room or the self may appear to be spinning even when sitting quietly. Disequilibrium refers to a sense of unsteadiness or imbalance. Dizziness is used by most people to refer to a wide range of symptoms including vertigo and simple lightheadedness. After some recovery time, vestibular symptoms usually subside but the person will continue to feel unsure and unsteady, particularly in reduced light conditions when visual information is minimal.

Box 10-9

THREE TISSUES PRODUCE FLUIDS THAT TOGETHER COMPRIZE TEARS.

Parasympathetic (from the facial nerve) and sympathetic (recall that sympathetic outflow emanates from cells in the thoracic spinal cord) nerves, as well as hormones, regulate tear composition and secretion. The lacrimal gland is most critical for the aqueous layer of tears, which is sandwiched between a hormone-regulated superficial lipid layer and a mucus layer secreted by the conjunctiva. When working correctly, irritation of the cornea, sensed by trigeminal neurons, stimulates lacrimal tear production. As the offending irritation increases in intensity, tear production increases. Should tear

production fail to match the need, the cornea is insufficiently protected and can become inflamed. Corneal inflammation can, in turn, overstimulate sympathetic innervation of the lacrimal glands, producing excessively watery tears and giving the rheumy appearance to eyes that is common among the elderly. In postmenopausal women, decreased levels of estrogen lead to a decline in hormonally driven tear production. If the lacrimal gland production is not sufficiently boosted to compensate, dry eye can result. In fact, dry eye is a common complaint among postmenopausal women.

Hair cells, non-neural sensory cells derived from placodes, are located in both the cochlea and the vestibulum. Those in the cochlea respond to sound, and those in the vestibulum respond to head acceleration. Full considerations of auditory and vestibular function are presented in Chapters 17 and 19, respectively.

THE GLOSSOPHARYNGEAL NERVE MULTITASKS IN CONCERT WITH THE VAGUS

The ninth and tenth cranial nerves—glossopharyngeal and vagus—emerge from the lateral edge of the medulla, with the glossopharyngeal rootlets lying immediately rostral to vagal rootlets. The glossopharyngeal nerve serves a hodgepodge of functions, with no single one of them dominating. It works in concert with the vagus nerve to protect the upper airway from undesirable foreign matter entering from above, as well as from aspiration of vomitus emerging from below.

The glossopharyngeal nerve carries motor innervation to the **stylopharyngeus muscle**, a skeletal muscle that elevates the pharynx during talking, swallowing, and vomiting or *emesis* (Table 10-3). Depending on the severity, impairment of glossopharyngeal innervation of the stylopharyngeus can have little effect or can result in difficulty swallowing, termed **dysphagia**, or talking, termed **dysarthria**. The glossopharyngeal nerve also contributes to salivation by targeting postganglionic parasympathetic neurons in the **otic ganglion** that control **parotid gland** secretions of saliva (Table 10-4).

BOX 10-10

BELL'S PALSY IS A RELATIVELY COMMON, AND TYPICALLY, TRANSIENT IMPAIRMENT OF FACIAL NERVE FUNCTION.

Bell's palsy is an infection or inflammation of the facial nerve that produces a transient weakness or paralysis of the muscles of facial expression. One of the cardinal signs of facial nerve paralysis is an absent or decreased **nasolabial fold** on the side of the lesion (see Fig. 10-10). The nasolabial fold is a deep wrinkle or fold that runs from the lateral edge of the nose to the lateral edge of the mouth. Since Bell's palsy affects all branches of the facial nerve, not just the motor control of the muscles of facial expression, it also can involve:

- Hyperacusis due to paralysis of the stapedius muscle
- Dry eye and dry mouth due to impairment of preganglionic parasympathetic nerves to lacrimal and salivary glands

- Pain radiating from the external ear through effects on the small number of sensory afferents carried in the facial nerve

Noticeable impairment of taste is less common. Bell's palsy typically remits spontaneously within some months. However, while the facial muscles are paralyzed or weakened, care must be taken to keep the eye on the affected side protected from either drying out or being injured by a foreign object, the latter danger heightened by the patient's inability to blink using the **orbicularis oculi** muscle.

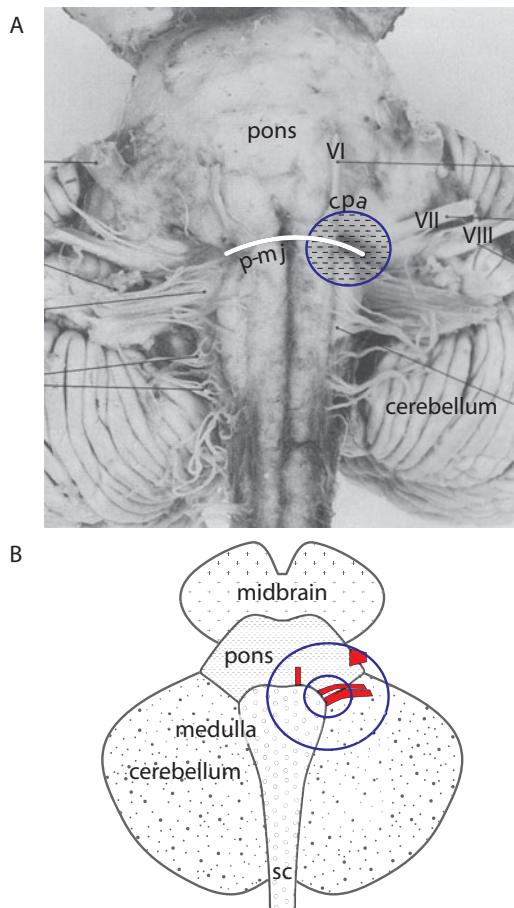
On the sensory side (Table 10-5), neurons from the **glossopharyngeal ganglia** travel in the glossopharyngeal nerve, carrying:

- somatosensory input from the middle ear, a small part of the external ear, the pharynx and the posterior third of the tongue
- taste information from the posterior third of the tongue and soft palate
- viscerosensory information about blood chemistry—oxygen levels, presence of nasty chemicals, pH, and the like—and blood pressure from the **carotid body**, a blood chemistry and pressure-sensing organ located in the neck.

Certain sensory information from all modalities carried in the glossopharyngeal nerve elicits protective airway reflexes, including but not limited to the **gag reflex**: an inedible foreign body touching the pharynx; rotten-tasting food; or the presence of **emetic** chemicals in the blood stream. Note that the sensory information carried by the glossopharyngeal nerve, outside of that arising from the external ear, may not reach conscious perception, as in the case of blood chemistry, and even if it does, is not discriminative in nature. In other words, we are unable to describe the texture and shape of something that touches the back of our pharynx even if we sense “something caught in the throat.” The vagus nerve also carries potentially emetic sensory input,

Figure 10-11. A: This photograph of the ventrum of the brainstem shows the cerebellopontine angle (*cpa*), which is located at the lateral edge of the pontomedullary junction (*white line labeled p-mj*) where cranial nerves VII and VIII emerge. B: A cartoon of the base of the brain illustrates the location of the cerebellopontine angle at the convergence of the cerebellum, pons, and medulla. The smallest tumors at the cerebellopontine angle cause hearing and balance problems. With progressively larger tumors, symptoms attributable to impairment of the facial, trigeminal and abducens nerves can also occur.

Photograph in A reprinted with permission from deArmond S., et al. *Structure of the human brain: A photographic atlas*. New York: Oxford University Press, 1989.



ACOUSTIC NEUROMAS FORM AROUND THE VESTIBULAR ROOT OF THE EIGHTH NERVE.

Acoustic neuromas are Schwannomas or tumors of Schwann cells (see Chapter 2) that are relatively common, occurring in 1 in 100,000 people. The majority of acoustic neuromas are **idiopathic** or **sporadic**, meaning that they happen to individuals who show no clear signs of susceptibility—they occur “out of the blue” and for no known reason. Most idiopathic acoustic neuromas are also benign. A notable exception to the benign and idiopathic nature of most acoustic neuromas occurs in patients with either of two types of **von Recklinghausen neurofibromatosis**, a pair of distinct dominant autosomal genetic diseases in which cell cycle control proteins, also known as **tumor suppressors**, are absent or defective. Patients with both types of neurofibromatosis are vulnerable to the development of a variety of tumors primarily in the skin and

nervous system. Patients with neurofibromatosis type II most often present with bilateral acoustic neuromas that are exceedingly rare under any other circumstance.

Regardless of the name, acoustic neuromas are neither acoustic nor tumors of neurons. Rather, the unfortunately named acoustic neuromas typically form in the Schwann cell lining at the root-nerve junction of the *vestibular* portion of the eighth cranial nerve. Thus, acoustic neuromas cause problems with equilibrium first and foremost. However, since acoustic neuromas form at a point near the cerebellopontine angle, progressively larger tumors eventually impair function of the cochlear component of cranial nerve VIII, as well as facial, glossopharyngeal, and even trigeminal nerves. Surgical removal is typically the preferred treatment.

as well as motor fibers necessary for protecting the upper airway from blockage (see more below).

SENSORY INPUT FROM AND PARASYMPATHETIC OUTPUT TO THE THORACIC AND ABDOMINAL VISCERA DEPENDS ON THE VAGUS NERVE

Vagal rootlets exit from the ventrolateral medulla for a stretch just caudal to the location of glossopharyngeal rootlets. In fact, the rootlets of cranial nerves IX and X form a continuous row with no clear demarcation between their exit points. The vagus nerve is the parasympathetic colossus, carrying preganglionic parasympathetic fibers to viscera in the thorax and abdomen including the lungs, larynx, heart, digestive tract from esophagus through midgut, and pancreas (Table 10-4). The vagus also innervates skeletal muscles of the pharynx and larynx (Table 10-3). Despite the diaspora-like parasympathetic projections of the vagus, *symptoms arising from vagal lesions are largely restricted to hoarseness, breathy speech, dysphagia, dysarthria, and compromised airway-protective reflexes, all of which depend on the relatively limited skeletomotor projections of the vagus.*

Broadly speaking, sensory fibers carried in the vagus nerve complement the functions provided by those in the glossopharyngeal nerve:

- somatosensory input from a small part of the ear, the pharynx, and the meninges of the posterior fossa (Table 10-5)
- taste information from the uvula and epiglottis (Table 10-2)
- viscerosensory information about blood chemistry and blood pressure from the aortic arch, a stretch of the aorta containing **baroreceptors**, or blood pressure-sensing cells (Table 10-5)
- viscerosensory information from the trachea, esophagus, epiglottis, lungs, heart, stomach, intestines, and other thoracic and abdominal viscera (Table 10-5).

Much of the vagally carried sensory information, along with that of the glossopharyngeal nerve, contributes to the detection of substances or objects that could occlude or damage the upper airway. Since rootlets of the two cranial nerves exit at adjacent sites, lesions that affect one of these nerves commonly also affect the other one. Such glossopharyngeal-vagal nerve lesions will affect upper airway function most profoundly and most obviously.

THE SPINAL ACCESSORY NERVE SUPPORTS HEAD GESTURES

The spinal accessory nerve emerges from the cervical spinal cord, but rather than exiting from the vertebral column, climbs up into the cranium, within the cerebrospinal fluid (CSF)-filled subarachnoid space, and then exits from the skull through the **jugular foramen**. This nerve provides motor innervation to two muscles: the **trapezius** involved in shrugging, and the **sternocleidomastoid** or **sternomastoid**, which turns the head as when shaking your head to indicate “no” (Table 10-3).

THE HYPOGLOSSAL NERVE CONTROLS TONGUE MOVEMENT

Hypoglossal rootlets exit from the base of the ventral medulla, close to the midline. The hypoglossal nerve innervates the muscles of the tongue, which are critical to breathing, eating, swallowing, speech, emesis, and a myriad of other functions such as communicating anger through a particularly immature gesture (Table 10-3). Isolated hypoglossal nerve injury or dysfunction is not a common occurrence.

DEDUCTIVE REASONING ALLOWS YOU TO NARROW DOWN THE POSSIBLE CAUSES OF SYMPTOMS INVOLVING CRANIAL NERVE FUNCTIONS

How does knowledge about the projections and functions of the cranial nerves help you figure out what is wrong with someone? Consider someone who complains of “not seeing right.” As you know by now, diplopia could result from a malfunctioning visual system or an impaired oculomotor, abducens, or trochlear nerve (see Box 10-12). Of these, oculomotor is a likely culprit as it innervates four muscles compared to the one apiece innervated by the abducens and trochlear nerves. Upon examination of the person’s eye movements—“follow my finger”—you may see, for example, that the right eye moves laterally and downward but does not move medially, toward the nose, or upward, adding to your suspicion that the oculomotor nerve, on the right side, is to blame for the diplopia. Such a finding provides impetus to test the remaining functions of the oculomotor nerve: voluntary eyelid elevation, pupillary constriction, and lens accommodation, any or all of which may be affected on the right side. If, on the other hand, you find that the right eye moves medially under some circumstances but not others, you would immediately know that the oculomotor nerve, *which cannot distinguish between circumstances*, is fine. In this case, the impairment must be within the CNS, which specializes in molding behavior to subtle differences in circumstances. Finally, consider if, upon exam, you find that the person has trouble moving both eyes in all directions, under all circumstances, but retains parasympathetic functions mediated by the oculomotor nerve. The likelihood of only the somatomotor portion of the oculomotor along with the abducens and trochlear nerves on both sides being knocked out by a single lesion is far less than the likelihood of winning the lottery just as you are being hit by a meteor, which is to say that it does not happen. Although not evident to the reader yet,

BOX 10-12

DIPLOPIA CAN RESULT FROM LESIONS IN A VARIETY OF LOCATIONS WITHIN AND OUTSIDE OF THE NERVOUS SYSTEM.

Lesions of all types—central, nerve, muscle—can produce diplopia. **Multiple sclerosis**, a central demyelinating disease, often impairs central connections that yoke voluntary but not reflexive lateral eye movements (much more on this in Chapter 26). **Oculomotor palsy**, which can result from any number of etiologies, impairs all third-nerve functions to a lesser or greater degree. Finally, a disease such as

chronic progressive external ophthalmoplegia, a mitochondrial muscle disorder, renders all skeletal muscles around the eye, extraocular and levator palpebrae alike, inoperative. This unfortunate disease eventually affects the long muscles of the limbs and torso, causing the patient great difficulty in standing and walking, as well as in eye movements.

the unlikelihood of a single central lesion giving rise to these symptoms rivals that of the single lesion impacting multiple nerves. Therefore, one thinks of a systemic disease, a disease whose skeletal muscle targets share a molecular vulnerability rather than a common location.



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CHAPTER 11

BRAINSTEM ORGANIZATION

THE BRAINSTEM SERVES FUNCTIONS FUNDAMENTAL TO LIFE

People without a functioning forebrain live, for a long time in some instances, but they do so without any meaning. The basic life that persists in the absence of the forebrain stems from the power of the brainstem. The brainstem sustains life even in the absence of meaningful experience, affording the physiological coordination necessary to keep breathing and beating one's heart (see Box 11-1). The brainstem is not luxurious, not optional, but rather fundamental, even if ordinary, and absolutely required. The brainstem also houses tracts that shuttle information between the forebrain and spinal cord as they necessarily traverse the brainstem en route to their destinations. In this chapter, we look from the outside at the brainstem in order to gain perspective on its functions and anatomical vulnerabilities.

Like the spinal cord, the brainstem also serves as a major conduit between the central nervous system and the periphery, in this case mostly serving tissues of the head. The conduit is formed by cranial nerves, which, while analogous to spinal nerves, come in more varieties: sensory, motor, and mixed (see Chapter 10). Even within the sensory and motor categories, the anatomical organization of the brainstem distinguishes subcategories. For example, motoneurons innervating somatic muscles, such as the tongue muscle, lie medial to motoneurons that innervate muscles derived from branchial arches, such as chewing muscles.

The medulla, pons, and cerebellum of the hindbrain along with the midbrain comprise the four major components of the adult brainstem (see Box 11-2). The hindbrain resembles the spinal cord in many respects. As introduced in Chapter 3, the hindbrain develops using the same fundamental principles as the spinal cord but differs in topology due to the opening of the fourth ventricle. The midbrain is separated during development from the hindbrain by a transient structure called the *isthmus*. The midbrain not only develops separately but has a different anatomical organization from that shared by the hindbrain and spinal cord.

As we move through the brainstem, we keep track of our three major pathways: the dorsal column-medial lemniscus, spinothalamic, and corticospinal

Box 11-1

THE BRAINSTEM SUSTAINS LIFE FOR PEOPLE IN A PERSISTENT VEGETATIVE STATE.

A person with a functioning brainstem, but without evident telencephalic function, is in a **persistent vegetative state**. Such an individual may wake and sleep and even move spontaneously but has no awareness of self or surroundings. Notably, this person is *not dead* according to the legal definition recommended by a presidential commission in 1981, and later adopted by most U.S. states: “An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the *entire brain*, including the brainstem, is dead.” By mandating

that the entire brain must be dead, this definition specifically excludes from death a person with residual brainstem function. However, instead of requiring proof that every neuron within the brain is dead, brain death or cessation of function in the entire brain is typically marked by: (1) loss of consciousness; (2) **apnea** or cessation of self-initiated breathing; (3) a lack of reaction to painful stimuli; and (4) no intact brainstem reflexes, such as the **corneal reflex**, in which stimulating the cornea elicits a reflexive blink.

Box 11-2

THE BRAINSTEM IS DEFINED HERE AS THE HINDBRAIN AND MIDBRAIN.

Some consider the diencephalon as part of the brainstem. However, in this book, we will use the slightly more common definition that the brainstem includes the hindbrain and midbrain but not the thalamus.

pathways. We also note where cranial nerve roots exit the brainstem. Finally, we focus on several structures too large and obvious to be ignored and more importantly, so visually remarkable as to provide easily recognizable landmarks.

MAJOR STRUCTURES INVOLVED IN MOVEMENT AND LIGHT TOUCH SENSATION ARE PRESENT IN THE MEDULLA

The medulla, the most caudal part of the brainstem, emerges from the spinal cord at the foramen magnum. Recall that the pyramidal decussation, or crossing of the pyramids, marks the spinomedullary junction (Fig. 11-1). The pyramids carry the corticospinal tract from the cerebral cortex down to the spinal cord. At the pyramidal decussation, synonymous with the motor decussation, corticospinal tract fibers cross from the side of their origin in motor cortex to the side of their destination in the ventral horn. The pyramidal decussation is apparent when viewing either a cross section (see Chapter 12) or the brain ventrum. Since the fibers cross at the midline and on the ventral surface, the pyramidal decussation appears as a blurring, or fusion, of the otherwise well-marked midline fissure (Fig. 11-1). *Above or rostral to the pyramidal decussation, voluntary motor commands travel contralateral to the muscles that they ultimately control. In contrast, caudal to the pyramidal decussation, voluntary motor commands travel ipsilateral to the targeted muscles.*

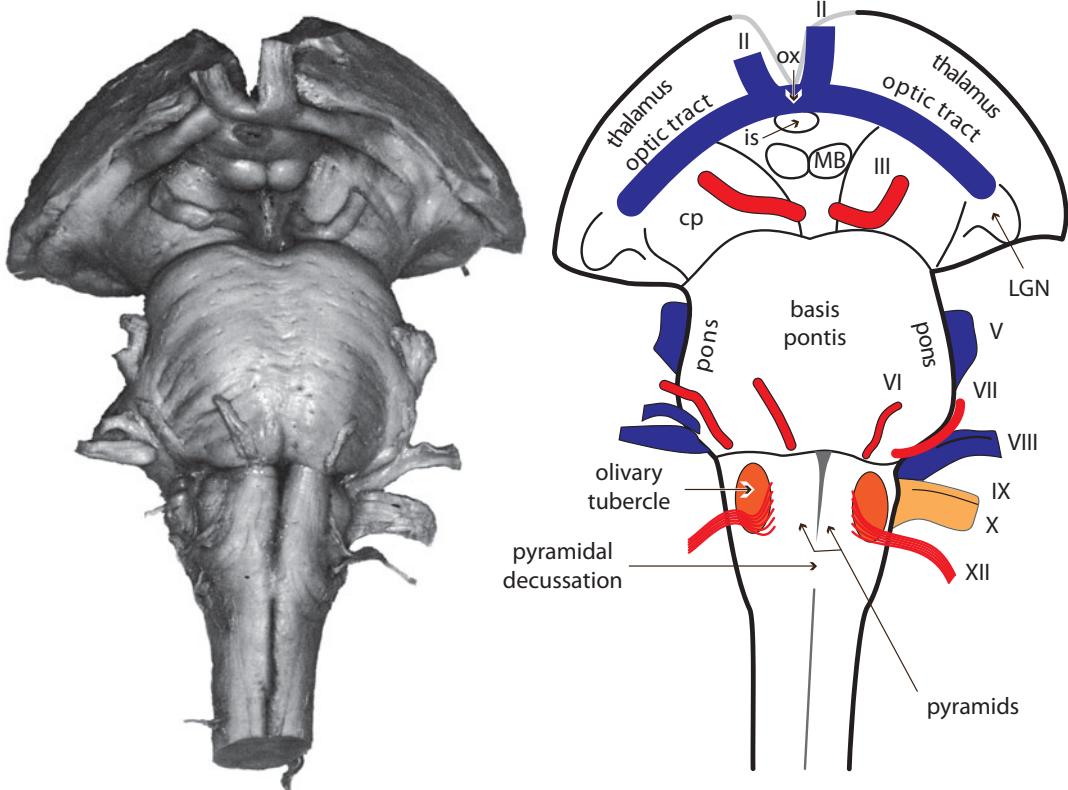


Figure 11-1. Major landmarks on the ventrum of the brainstem and diencephalon are shown in photographic (left) and diagrammatic (right) forms. The spinomedullary junction is marked by the pyramidal decussation, which appears as a blurring of the midline. At the pyramidal decussation, most of the corticospinal fibers in the medullary pyramids cross the midline to travel in the lateral corticospinal tract of the spinal cord. Beyond the prominent pyramids, the medullary ventrum is also marked by the olfactory tubercles, bumps that overlie the precerebellar olfactory nuclei. Hypoglossal nerve (XII) rootlets emerge between the lateral edge of the pyramid and the medial edge of the olfactory tubercle, whereas glossopharyngeal (IX) and vagal (X) roots emerge from the lateral edge of the rostral medulla. The pontomedullary junction is marked by the emergence of three pairs of cranial nerves. Recall from Chapter 3 that motor structures are located medial to sensory structures in the brainstem. Consistent with this organizational principle, the abducens nerve (VI) emerges from near the midline while the vestibulocochlear nerve (VIII) emerges at the laterally located cerebellopontine angle. The facial nerve (VII) is a mixed cranial nerve and emerges laterally after taking a peculiar course through the brainstem (see Chapter 12). The trigeminal nerve (V), the largest cranial nerve, exits from the lateral surface of the pons. The pons is marked ventrally by the bulbous basis pontis that houses the pontine nuclei. Since information from motor cortex always synapses in the pontine nuclei before reaching the cerebellum, the sizes of the frontal cortex, basis pontis, and cerebellum are coordinated, reaching a zenith in animals such as humans who have a rich repertoire of complex fractionated movements. Rostral to the basis pontis, the midbrain is marked by the presence of the cerebral peduncles (cp), a large white matter tract that carries information from the forebrain to the brainstem and spinal cord. The oculomotor roots emerge from the medial edge of the cerebral peduncles and consist of somatomotor and parasympathetic motor input to the orbit. The transition between the midbrain and diencephalon is an irregular line. Caudal diencephalic structures include the mammillary bodies (MB), lateral geniculate body or nucleus (LGN), and the optic tract. The infundibular stalk (is), optic chiasm (ox), and optic nerves (II) are also prominent in this view.

Photograph reprinted with permission from deArmond S., et al. *Structure of the human brain: A photographic atlas*. New York: Oxford University Press, 1989.

Just lateral to the pyramids at the base of the medulla, bumps called the **olivary tubercles** indicate the location of the **inferior olivary nuclei** or **inferior olives** (Fig. 11-1). The inferior olives, unrelated to any cranial nerve but distinctive landmarks of the caudal medulla, provide an important signal that teaches the cerebellum how to make an intended movement correctly and smoothly (see Chapter 24). Between the olivary tubercles and the pyramids, a set of rootlets emerges from the medulla (see Box 11-3).

ROOTLETS COALESCE INTO A ROOT, WHICH BECOMES A NERVE UPON EXITING THE DURAL SHEATH.

We saw in the spinal cord that axons exit as rootlets and then coalesce into a root. The same pattern is seen in the brainstem. Upon exiting the brainstem, fascicles of axons form many small rootlets. Multiple rootlets destined for one cranial nerve coalesce to form a root. This pattern of many rootlets emerging from the brainstem is particularly evident for the hypoglossal, vagal and glossopharyngeal nerves.

and Fig. 11-1). These rootlets coalesce into the hypoglossal nerve destined for the muscles of the tongue. Farther laterally, a long line of rootlets emerges, most of which converge to form the vagus nerve. The most rostral rootlets merge to become the glossopharyngeal nerve. Off the side of the medulla, the large and well-myelinated spinal accessory nerve root travels from the cervical spinal cord into the skull before exiting through the jugular foramen.

Upon viewing the medulla from the dorsum, one sees that the dorsal columns of the spinal cord continue seamlessly into bumps that contain the dorsal column nuclei, where primary afferents carrying information about ipsilateral light touch, vibration, and proprioception terminate (Fig. 11-2). The dorsal column nuclei are visible as the **tubercls gracilis**, located medially, and the **tubercls cuneatus**, located laterally and a bit rostrally. Each of these tubercles represents the external manifestation of the underlying eponymous nucleus, receiving its input from the fasciculus of the same name. Thus, light touch, vibration, and proprioceptive information from the ipsilateral leg and lower trunk travel through the fasciculus gracilis to the nucleus gracilis, also termed the gracile nucleus, which is viewed from the outside as the tubercle gracilis. Similarly, tactile and other low-threshold information arising from the upper trunk and arms travels in the fasciculus cuneatus to reach the nucleus cuneatus or cuneate nucleus, which is visible from the outside as the tubercle cuneatus. Within the dorsal column-medial lemniscus pathway, *the dorsal column nuclei represent the first central synapse for information about light touch, vibration, and proprioception from the same side of the body*.

The central canal, patent in fetal life but occluded after birth, moves to a progressively more dorsal position within the cervical spinal cord until it reaches the dorsal surface and opens up into the fourth ventricle. Although initially covered by overlying medullary tissue, the fourth ventricle opens to form the space between the medulla and the cerebellum at a point rostral to the spinomedullary junction. The point of ventricular opening, termed the **obex**, forms the most caudal point of the rhomboid fossa, the diamond-shaped floor of the fourth ventricle (Fig. 11-2). Only when the cerebellum is removed is the diamond-shape revealed with the obex as the caudal point of the diamond. External structures rostral to the obex follow the margins of the rhomboid fossa rather than aligning purely along linear rostral-caudal lines. For example, the tubercles gracilis and cuneatus veer laterally as they extend rostrally, hugging the outline of the widening rhomboid fossa (see Box 11-4).

The axons of cells in the dorsal column nuclei immediately cross the midline to form the **medial lemniscus**, a tract that takes light touch information to the contralateral thalamus. This crossing of light touch, vibration, and proprioceptive information, sometimes termed the sensory decussation, is only visible in cross-sections and occurs at the level of the gracilis and cuneatus tubercles (see Chapter 12). Note that the sensory decussation only refers to the crossing of a portion of somatosensory input; as you recall, afferents carrying pain and temperature information cross the midline within the spinal cord (see Chapter 9). Knowing the level of the sensory decussation holds the same deductive promise as knowing the level of the motor decussation. Specifically, lesions to the dorsal columns or dorsal column nuclei, below the level of the sensory decussation, will compromise sensations of light touch on the ipsilateral side, whereas lesions rostral to the sensory decussation will compromise dorsal column-mediated sensations contralaterally.

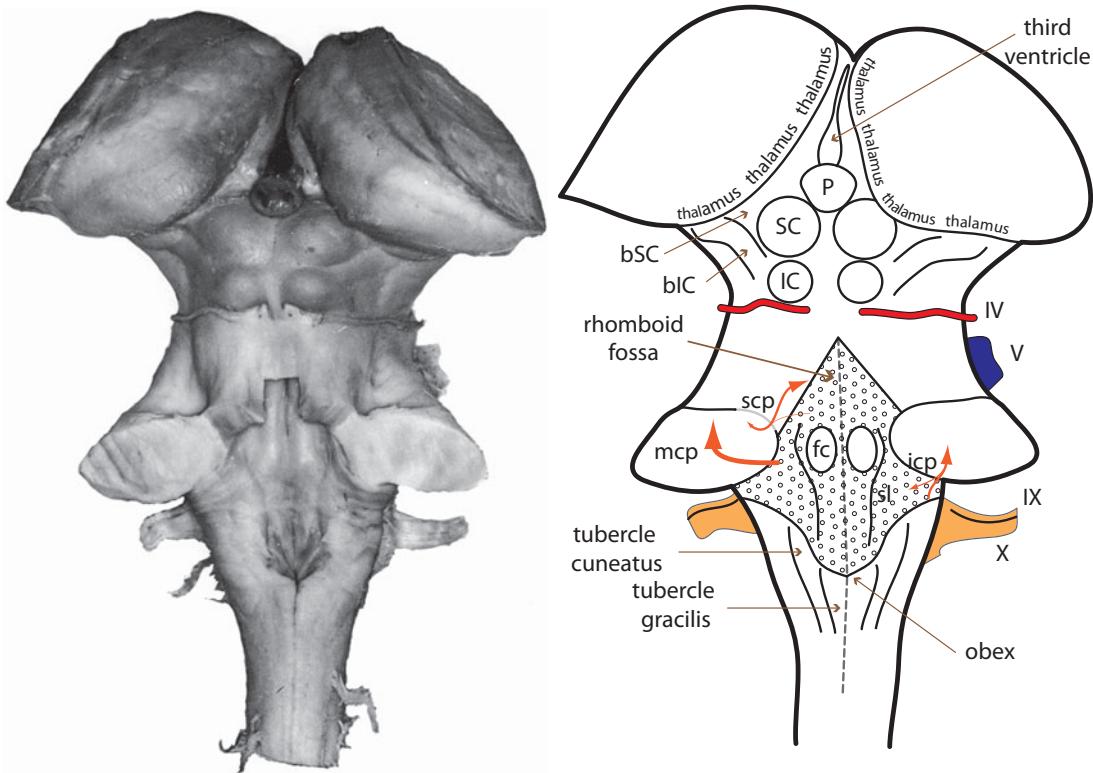


Figure 11-2. Major landmarks on the dorsum of the brainstem and diencephalon are shown in photographic and diagrammatic forms. The brainstem was isolated by removing the telencephalon and the cerebellum. None of the surfaces illustrated are open to view in the intact brain. The medulla is marked by the tubercles cuneatus and gracilis, which are bumps located at the site of the dorsal column nuclei. Recall that the nuclei cuneatus and gracilis are the site of the first synapse in the dorsal column-medial lemniscus pathway, which carries tactile information from the same side of the body. The obex is the caudal-most point in the rhomboid fossa (*patterned area*), the cavity of the fourth ventricle. Note that the anterior portion of the rhomboid fossa is obscured in the photograph at left by the overlying **medullary velum** or veil, a thin non-neuronal tissue that forms the roof of the fourth ventricle. The facial colliculi (*fc*), where facial motoneuron axons make a hairpin turn around abducens motoneurons (see Chapter 12), are located on either side of the pontine midline. Lateral to the facial colliculi are the sulci limitans (*sl*), small indentations in the floor of the fourth ventricle that demarcate the border between sensory and motor nuclei. The pons is delimited by the cerebellar peduncles, which were cut transversely to prepare this isolated brainstem. The middle cerebellar peduncles (*mcp*), containing cerebellum-destined axons from the basis pontis, occupy most of the cut surface. The inferior cerebellar peduncles (*icp*) primarily contain axons entering the cerebellum from the medulla and the spinal cord and a smaller number of cerebellar efferents bound for hindbrain targets. The superior cerebellar peduncles (*scp*) primarily consist of axons leaving the cerebellum for the midbrain and diencephalon but also contain a small number of afferents from the spinal cord. The trochlear nerves (IV) exit from the dorsal surface of the brainstem at the junction between the pons and midbrain. The dorsal surface of the midbrain is marked by four prominent bumps: the inferior and superior colliculi (IC, SC). Both colliculi send axons to the thalamus via an arm or brachium. The brachium of the inferior colliculus (*bIC*) is clearly visible, but the brachium of the superior colliculus (*bSC*) is mostly hidden in this photograph. The diencephalon is marked by the pineal gland (*P*), the third ventricle, and the thalamus. The roots of cranial nerves V, IX, and X are prominent in this preparation and are marked.

Photograph reprinted with permission from deArmond S., et al. *Structure of the human brain: A photographic atlas*. New York: Oxford University Press, 1989.

MOTOR STRUCTURES DOMINATE THE EXTERNAL LANDSCAPE OF THE PONS AND CEREBELLUM

The cerebellum, Latin for *little brain*, sits separately from the brainstem, linked only by the cerebellar peduncles, large bundles of axons that attach the cerebellum to the brainstem (Fig. 11-2). Three individually named peduncles join

EXTERNAL MEDULLARY LANDMARKS INCLUDE STRUCTURES CARRYING VOLUNTARY MOVEMENT COMMANDS, LIGHT TOUCH SENSORY INPUT, AND AN IMPORTANT PRECEREBELLAR NUCLEUS.

Pyramidal decussation (ventral midline at spinomedullary junction) is the site where corticospinal tract axons cross the midline from the side of cortical origin to the side of spinal destination.

Pyramids (straddle the ventral midline for the length of the medulla) contain the corticospinal tract, carrying a voluntary movement signal from motor cortex to motoneurons in the spinal cord that innervate muscles on the contralateral side.

Olivary tubercles (ventral, just lateral to the pyramids) contain the inferior olfactory nuclei, a major source of motor and sensory input to the cerebellum.

Tubercl gracilis (runs along the lateral edge of the rhomboid fossa) contains the nucleus gracilis,

which receives light touch information from the ipsilateral leg and lower trunk via the fasciculus gracilis.

Tubercl cuneatus (abuts the lateral edge of tubercle gracilis) contains nucleus cuneatus, which receives light touch information from the ipsilateral arm and upper trunk via the fasciculus cuneatus.

Obex (caudal midpoint of the rhomboid fossa on the dorsal surface of the medulla) is the point where the central canal opens up into fourth ventricle.

Rhomboid fossa (ventricular space covering the dorsum of most of the medulla and all of the pons) is the diamond-shaped cavity occupied by the fourth ventricle.

each other to form a large peduncle, Latin for *stalk*, consisting of millions of fibers, connecting the cerebellum with the brain and spinal cord on each side:

- The **inferior cerebellar peduncle** contains fibers connecting the cerebellum with the spinal cord and medulla.
- The **middle cerebellar peduncle**, or **brachium pontis**, constitutes the bulk of the connection linking the cerebellum with the brainstem. The middle cerebellar peduncle carries fibers from neurons in the basis pontis destined for the cerebellum.
- Finally, fibers exiting the cerebellum to reach midbrain and diencephalic targets make up the bulk of the **superior cerebellar peduncle** or **brachium conjunctivum**.

The inferior and superior cerebellar peduncles are far smaller than the middle cerebellar peduncle and are most easily visualized in cross-section (see Chapter 12). The enormous middle cerebellar peduncles roughly delimit the rostrocaudal extent of the pons. About midway through the pons, two small bumps straddle the midline. These bumps are the **facial colliculi**. The facial colliculi mark where motor axons that control the muscles of facial expression wrap around a nucleus containing neurons that control lateral eye movement (see Box 11-5).

PONTINE LANDMARKS MAINLY REVOLVE AROUND CONNECTIONS WITH THE CEREBELLUM.

Basis pontis (ventral for the length of the pons) is the base of the pons that contains corticospinal tract axons that control voluntary movements on the opposite side.

Middle cerebellar peduncle (cut surface lateral to the rhomboid fossa) is one of three connections between the brainstem and the cerebellum. The middle cerebellar peduncle, the largest of the peduncles, is part of a pathway from cerebral cortex to the basis pontis and from basis pontis to the cerebellum.

Inferior cerebellar peduncle (caudal portion of the cut peduncles) primarily carries input from the spinal cord and inferior olives into the cerebellum. The inferior cerebellar peduncle also carries output from the cerebellum to the hindbrain, which is involved in balance, gait, and other midline movements including speech articulation.

Superior cerebellar peduncle (rostral portion of the cut peduncles) primarily carries output from the cerebellum destined for midbrain and forebrain.

Facial colliculus (on the floor of the fourth ventricle, halfway through the pons and on either side of the midline) is a bump formed by axons of facial nerve motoneurons, which control facial expressions, as they curve around the **abducens nucleus** that gives rise to the abducens nerve and controls lateral eye movement.

The convexity of the base of the pons, termed the basis pontis, delimits the pons ventrally (Fig. 11-1). The basis pontis contains the resident **pontine nuclei** and the corticospinal fibers traversing through. Recall that the pons is rostral to the motor decussation. Therefore, *fibers within the basis pontis destined for the lateral corticospinal tract are ipsilateral to the cortex from which they arose but contralateral to the neurons and muscles that they ultimately influence*. As the corticospinal fibers cross the pons en route to the spinal cord, they send an axon collateral, with a copy of their message about intended movements, to neurons in the pontine nuclei (Fig. 11-3). Neurons in the pontine nuclei in turn send this message across the midline and into the cerebellum via the massive middle cerebellar peduncle. In this way, the cerebellum receives information about all the movements that cortex is commanding, planning to initiate, or even just considering. As we shall see in Chapter 24, the cerebellum coordinates the movements of multiple muscles across multiple joints and ensures that the movements we make are smooth and constitute those that we intend to make. Across vertebrate phylogeny, the cerebellum and basis pontis become increasingly involved, and progressively larger, as an animal's movement repertoire grows more sophisticated. Since the middle cerebellar peduncle consists entirely of axons coming from the basis pontis and entering the cerebellum, the size of the middle cerebellar peduncle grows in concert with the size of the basis pontis and cerebellum. In humans and other animals capable of complex movements, the middle cerebellar peduncle, basis pontis, and cerebellum are all far larger than in animals capable of less intricate movements.

THERE IS FAR MORE INPUT TO THE CEREBELLUM THAN OUTPUT FROM IT

As you recall, the cerebellum develops from the anterior rhombic lip, and in the adult, covers the fourth ventricle, which itself sits atop the pons and rostral medulla. The cerebellum would be an island were it not for the three pairs of cerebellar peduncles. Therefore, *all input to and output from the cerebellum travel in one of the three cerebellar peduncles*. Because of the cerebellum's isolation and consequent dependence upon the peduncles for communication with the rest of the brain, damage to any of the cerebellar peduncles has profound effects, akin to those produced by damage to the cerebellum itself.

The inferior cerebellar peduncle carries mostly sensory input from the spinal cord, the middle cerebellar peduncle carries input from pons, and the superior cerebellar peduncle carries most of the output from the cerebellum. The far greater girth of the middle cerebellar peduncle than the superior cerebellar peduncle nicely illustrates the gross imbalance between input to and output from the cerebellum. *The number of axons entering the cerebellum is 40 times greater than the number exiting, reflecting the cerebellum's extraordinary processing capacity to compute one solution when provided with a multitude of inputs.*

THE CEREBELLUM CONTAINS MULTIPLE, FUNCTIONALLY DISTINCT REGIONS

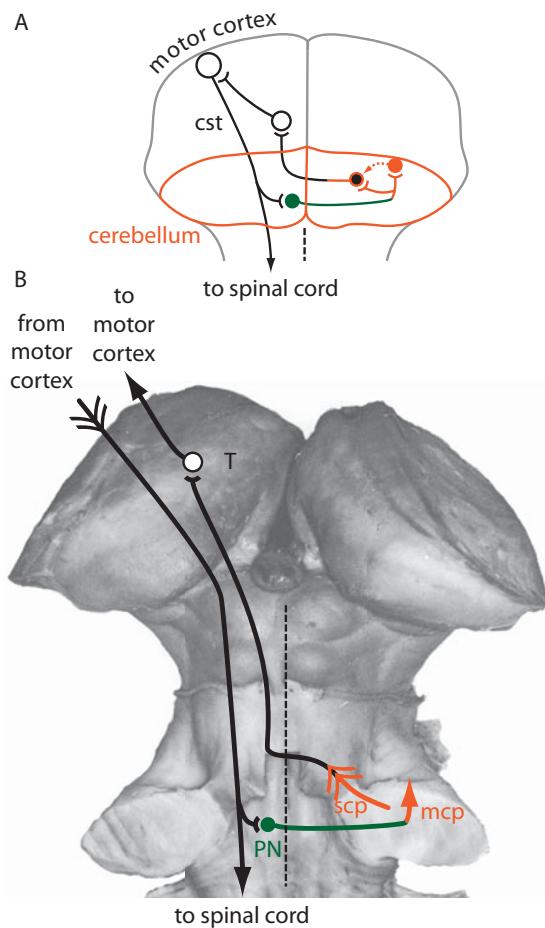


Figure 11-3. Although the motor cortex is critical to the initiation of voluntary movements, the cerebellum is needed to ensure that multijoint movements are smooth and coordinated. The cerebellum modifies the movements produced by motor cortex through a neural circuit that is diagrammed here. Neurons in motor cortex project to the spinal cord through the corticospinal tract (*cst*). Corticospinal axons send collaterals to synapse on neurons in the pontine nuclei of the basis pontis. Pontine nuclear neurons (*PN*) in turn send an axon, a type of mossy fiber, across the midline and into the cerebellum (orange colored cells and axons) through the middle cerebellar peduncle (*mcp*). The pathway from motor cortex to pons to cerebellum enables the cerebellum and spinal cord to receive similar messages from motor cortex. The cerebellum processes information (dotted line in A) about intended movements, and its “verdict” is carried by the output neuron of the cerebellum (black centered neuron in A) through the superior cerebellar peduncle, across the midline, and to the thalamus (*T*). Thalamic neurons that receive input from the cerebellum project back to motor cortex. Through the circuit described and illustrated here, the cerebellum receives information about intended movements and can modify the actual movements produced. Note that the cerebellum and the contralateral motor cortex work together to coordinate voluntary movements that are *ipsilateral* to the cerebellar neurons involved. In the example illustrated here, the left motor cortex and right cerebellar hemisphere influence voluntary movements on the right side of the body. Photograph in B reprinted with permission from deArmond S., et al. *Structure of the human brain: A photographic atlas*. New York: Oxford University Press, 1989.

The cerebellum consists of three regions that are organized along rostral caudal lines. The midline **vermis** is flanked by two laterally-situated **hemispheres** or **lobes** (Fig. 11-4). The most medial portion of each cerebellar hemisphere is termed the **paravermis**, and the lateral portions of the lobes are simply called the **lateral lobes**. The vermis and paravermis together are critical to the orchestration of movements that span more than one joint, ensuring that the movements are smooth and finish on target. The lateral lobes are critical to coordinating visually guided movements and to learning complex new movements. For example, when learning to play a new sport or a new instrument, we repeat and repeat and repeat. Our initial attempts are uncoordinated and slow but after more repetition, a sequence of awkward movements is transformed into one smooth, fluid action. The lateral lobes are critical to that magical transformation.

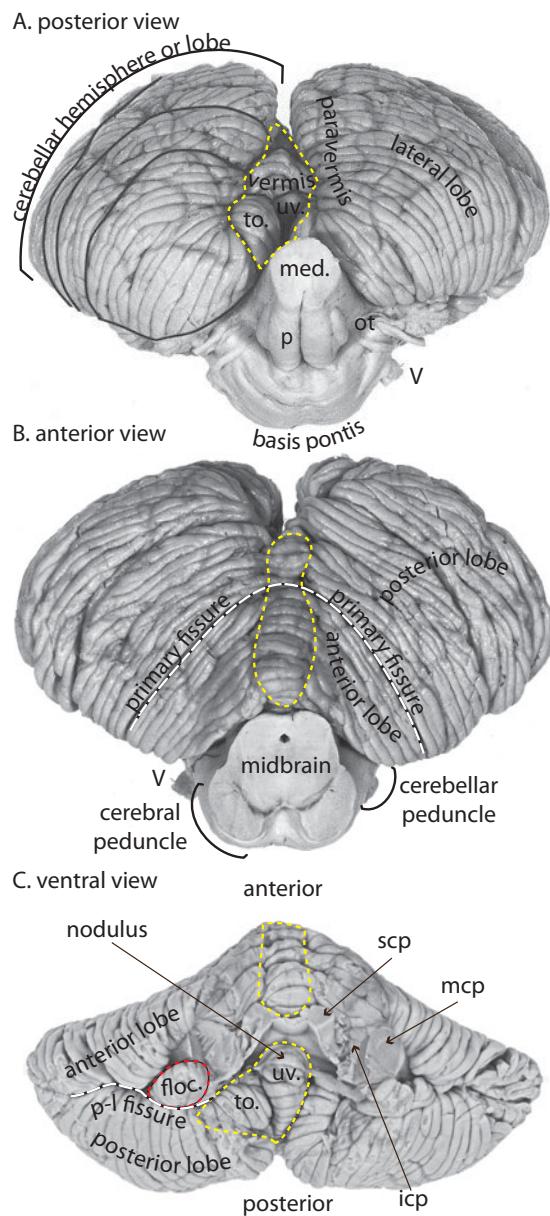
The **pathognomonic**, or defining characteristic of, damage to the cerebellum is **ataxia**. Ataxia is a distinctive form of uncoordinated movement that uses successive corrections to reach a target (Fig. 11-5). Ataxic movements are slow. Ataxic movements are also decomposed into their component parts. In

place of one smooth, fluid action, a series of uncoordinated movements occurs.

The **flocculonodular lobe** includes the **flocculus** within the hemisphere and the **nodulus** within the vermis. Along with the vermal **uvula**, the flocculus and nodulus are critical to the coordination of maintaining balance, eye movements, and visually

Figure 11-4. Three views of the cerebellum are shown, with major parts labeled. Viewed from the rear (A), it is clear that the large cerebellar hemispheres or lobes overwhelm the cerebellar vermis, which lies hidden deep between the hemispheres. The vermis (yellow dashed line) contains the tonsil (to. in A and C), uvula (uv. in A and C), and nodulus (C only). The cerebellar vermis is unusual in that it is asymmetric, a feature that is evident in these photographs. The medial part of each hemisphere is termed the paravermis. When the cerebellum is viewed from the front (B), the primary fissure (dashed white line) that separates the cerebellum into anterior and posterior lobes is visible. When the cerebellar peduncles are cut, the cerebellum can be viewed from the underside (C). From this vantage point, the flocculus (floc.), the hemispheric portion of the flocculonodular lobe, and the nodulus, the vermal portion of the flocculonodular lobe, can be seen. The posterolateral fissure (p-l fissure) separates the anterior and posterior lobes ventrally. It also separates the posterior lobe from the flocculus. The inferior (icp), middle (mcp), and superior (scp) cerebellar peduncles can be distinguished from the ventral side. Additional features labeled for orientation include the medulla (med.), p (pyramidal), olivary tubercle (ot), trigeminal nerve (V), midbrain, and cerebral peduncle.

Photographs reprinted with permission from Bruni, J.E., and Montemurro, D. *Human neuroanatomy: A text, brain atlas, and laboratory dissection guide*. New York: Oxford University Press, 2009.



guided movements. The flocculonodular lobe is critical to adjusting to new viewing conditions, such as eyeglasses with a new prescription. Damage to the flocculonodular lobe can have devastating effects on a person's ability to feel balanced and steady in the world (see Chapter 26). Damage to the cerebellar hemispheres lateral to the paravermis also results in problems with balance, eye movements, and visually guided movements—problems associated with floccular function as well, but not in trunk or limb ataxia. In place of overt ataxia, hemispheric damage may cause subtle deficits in learned, skilled movements.

Fissures—large, medium, and small—characterize the surface of the cerebellum. The largest fissure, the **primary fissure** located on the dorsum of the cerebellum, divides the **anterior** and **posterior lobes** (Fig. 11-4B). The **posterolateral fissure**, located ventrally, divides the posterior lobe from the flocculus, which abuts the

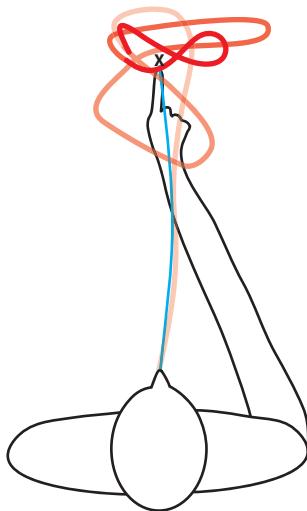


Figure 11-5. When asked to touch the nose and then a target (X), a physician's finger for example, at arm's reach, a neurologically normal individual makes a direct trajectory (blue line) to the target. When an individual with a cerebellar lesion, particularly one in the vermis or paravermis, is asked to perform the same task, the patient's finger traces a far more circuitous route to the target (red line). Lines in progressively darker shades of red depict successive moments in time. Deviations from a normal trajectory increase in frequency and magnitude as the finger approaches the end target. This type of uncoordinated movement is termed *ataxia* and is pathognomonic for cerebellar damage. In addition to traversing a roundabout path, ataxic movements are slower than normal ones. Whereas normally touching a target at arm's reach is accomplished in about a second, ataxic patients take well more than a second to just reach the vicinity of the target. They then require several more seconds to approach the target more closely and have great difficulty holding their finger stationary at the target.

middle cerebellar peduncle (Fig. 11-4C). In a sagittal section, the lobes appear like bushes, with the branches being **lobules**, which in turn consist of twig-like **folia** (Fig. 11-6A). The number and pattern of lobules are remarkably consistent across individuals and mammalian species, such that the lobules are labeled I–IX from rostral to caudal. The folia consist of countless superficial folds oriented transversely and covering the entire cerebellar surface.

The cerebellum, like the cerebrum, contains a mantle or rind of layered cells that comprise a cortex (more on this in Chapter 13). The folia increase the surface area of the cerebellar mantle and serve an analogous function as sulci and gyri, which increase the area of the cerebral mantle. The expanded cerebellar surface area houses the enormous **cerebellar cortex** (Fig. 11-6B). Deep to the cerebellar cortex is cerebellar white matter, containing axons that bring information to and take information from the cerebellar cortex.

COLLICULI CAP THE MIDBRAIN AND CEREBRAL PEDUNCLES FLANK THE BASE OF THE MIDBRAIN

The basis pontis ends abruptly at the **pontomesencephalic junction**, where the midbrain's cerebral peduncles take over the ventral surface (Fig. 11-1).

The cerebral peduncles carry axons traveling from the forebrain to the brainstem and/or the spinal cord. Fibers of the corticospinal pathway travel in the middle portion of each cerebral peduncle, contralateral to the side of the muscles that they ultimately control.

Also present at the anterior edge of the midbrain ventrum is the **optic tract**, containing axons from the retina destined for the thalamus (Fig. 11-1). The optic tract wraps around the anterior and lateral edges of the cerebral peduncles. Because of their anatomical proximity, these two elements, the cerebral peduncle and the optic tract, are often damaged by a single injury. The result is impairment of two very different functions: *contralateral voluntary movement and vision of the contralateral visual field, a combination that is pathognomonic for a midbrain lesion*. Rootlets of the oculomotor nerve destined to control most eye movements (see Chapter 10) emerge from the medial edge of the cerebral peduncles in the caudal midbrain (Fig. 11-1). Just rostral to

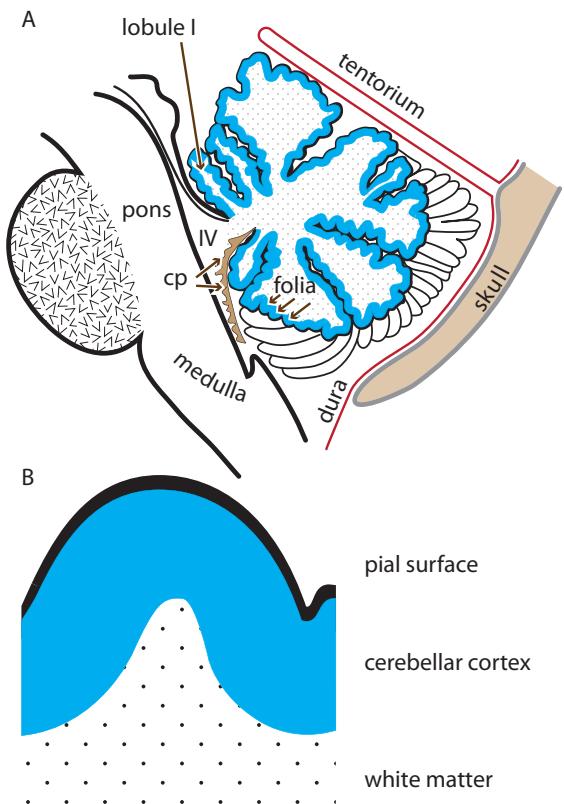


Figure 11-6. A: The cerebellum consists of nine lobules or branches, with lobule I being the most anterior of the lobules. The lobules can be clearly seen in a sagittal section. Folia are the smallest divisions of the cerebellum, appearing like twigs off of the lobules. The fourth ventricle (IV) occupies the space between the cerebellum and the pons and rostral medulla. In the caudal portion of the roof of the fourth ventricle, choroid plexus (cp), the non-neural tissue that makes cerebrospinal fluid (CSF), is present. The tentorium, a fold of dura, separates the cerebellum from the occipital cortex. B: Cerebellar neurons are concentrated in cortical layers along the outer edge of the cerebellum. Thus, throughout the cerebellum, cerebellar cortex lies just beneath the pial surface. Deep to the cerebellar cortex is white matter.

Drawing in A adapted with permission from deArmond S., et al. *Structure of the human brain: A photographic atlas*. New York: Oxford University Press, 1989.

the **mesodiencephalic junction**, the junction of the midbrain and diencephalon, are the mammillary bodies located at the caudal pole of the hypothalamus.

As introduced in Chapter 3, four colliculi occupy the dorsal surface of the midbrain (Fig. 11-2). Altogether, the four colliculi, bilateral pairs of inferior and superior colliculi, are sometimes referred to as the **corpora quadrigemina**, Latin for *four bodies*. The inferior colliculi are important to localizing sounds and are an essential way-station in the auditory pathway. Localizing sounds is a very important function for animals who must capture prey and/or avoid predators in order to survive. Sound localization is *not* a big part of modern human life and clinical complaints regarding this faculty do not occur.

Like the inferior colliculi, the superior colliculi, often referred to as the **tectum**, participates in stimuli localization. The superior colliculi are most important to localizing **visual** stimuli. The superior colliculi coordinate orienting movements of the eyes and head toward unexpected sights and sounds as well. So, whether someone rings a doorbell or waves frantically, you will use your superior colliculus to turn to the source of the greeting. Although the superior colliculi are not part of the

pathway for conscious visual perception, they can contribute to subconscious perception. In fact, the superior colliculi are responsible for **blindsight**, in which people with an impaired visual cortex are able to orient to objects with their eyes. They orient to unexpected images, such as a fireworks blast, even though they cannot *perceive* the objects that they turn to gaze at (see Chapter 16).

Neurons in both the superior and inferior colliculi project to the thalamus, to caudal thalamic nuclei located just rostral to the mesodiencephalic border. The connecting fibers travel superficially, making visible “arms” or **brachia** (**brachium** is the singular) where they run on the dorsolateral surface of the brain (Fig. 11-2). The **brachium of the inferior colliculus** carries auditory information from the inferior colliculus to the **medial geniculate nucleus** or **medial geniculate body** of the thalamus. The **brachium of the superior colliculus** carries visual information from the superior colliculus to the lateral geniculate nucleus, also termed **lateral geniculate body**, of the thalamus (see Box 11-6). Both the medial and lateral geniculate bodies form small bumps on the lateral surface of the thalamus.

THE INFERIOR AND SUPERIOR COLICULI MARK THE MIDBRAIN DORSALLY, AND THE CEREBRAL PEDUNCLES FORM THE VENTRUM OF THE MIDBRAIN.

Inferior colliculi (caudal bumps on the dorsal midbrain surface) are part of the auditory pathway.

Superior colliculi (rostral bumps on the dorsal midbrain surface) are important in coordinating orienting movements of the eyes, head, and trunk.

Cerebral peduncles (ventral tracts) carry axons traveling from the forebrain to the hindbrain and spinal cord, including the corticospinal and corticopontine tracts.

Brachium of the inferior colliculus (a protuberance extending rostrally and laterally from the inferior colliculus) connects the inferior colliculus to the medial geniculate body of the thalamus.

Brachium of the superior colliculus (a protuberance extending rostrally and laterally from the superior colliculus) connects the superior colliculus to the lateral geniculate body of the thalamus.

The midbrain gives way to the thalamus at the mesodiencephalic junction, marked by the optic tract ventrally and the pineal gland dorsally. The pineal gland, a non-neural gland that secretes **melatonin** and is important in biological rhythms, sits in a midline recess at the anterior pole of the superior colliculi (Fig. 11-2). The **posterior commissure** also marks the mesodiencephalic junction and is visible as a white matter tract on the dorsal surface of the brain just ventral to the pineal gland. Because it is easily visualized by noninvasive scanning techniques, the posterior commissure is an important landmark for brain imaging.

THE BRAINSTEM CRANIAL NERVE NUCLEI ARE THE SOURCE OR TARGET OF THE TEN BRAINSTEM CRANIAL NERVES

Within the spinal cord, neurons are clustered within a central gray region surrounded by white matter. In contrast, most brainstem neurons collect within globular nuclei that sit interspersed with other nuclei. Within the central core of the brainstem, nuclei are marked by the presence of criss-crossing axons that lend a net-like or **reticulate** appearance to the area. Regions with such a reticulated appearance comprise the **reticular formation** or **tegmentum**, which stretches from the medulla to the midbrain. The reticular formation contains neurons that serve fundamental, phylogenetically conserved homeostatic functions, such as the control of blood pressure and level of arousal.

Beyond nuclei of the reticular core, most brainstem nuclei contain neurons directly associated with cranial nerves or neurons that provide direct cerebellar input. Nuclei containing the neurons that connect with cranial nerves are termed **cranial nerve nuclei**. Cranial nerve nuclei include a diverse group of sensory and motor nuclei. Here, we introduce the cranial nerve nuclei, each of which will be discussed at least one more time in future chapters. In this section, we focus on the brainstem cranial nerves III through XII. The olfactory bulb is the recipient of input from cranial nerve I. The connections of the optic nerve are considered in detail in Chapter 16.

The sensory nuclei include:

- Two somatosensory nuclei (**main** or **principal sensory nucleus**, **spinal trigeminal nucleus**) are associated with afferent input from the face that travels primarily through the trigeminal nerve with smaller contributions from VII, IX, and X.
- A viscerosensory nucleus, the **nucleus of the solitary tract** or **nucleus tractus solitarius**, receives both gustatory and viscerosensory information, the latter from the viscera above the hindgut. Most of the input is vagal (X), with smaller contributions from VII and IX.

- **Vestibular nuclei** receive input from the vestibulocochlear nerve about the movement and position of the head.
- **Cochlear nuclei** receive auditory input from the cochlea via the vestibulocochlear nerve.

Note that the eighth cranial nerve carries information from sensory neurons in the inner ear. Since the inner ear derives from the otic placode, balance and hearing are considered **special senses** rather than somatic senses.

Cranial motor nuclei can be divided roughly into three groups:

- Somatomotor nuclei contain motoneurons innervating the tongue and extraocular muscles:
 - The **hypoglossal nucleus** contains motoneurons innervating the tongue.
 - The **abducens, trochlear, and oculomotor nuclei** contain motoneurons innervating extraocular muscles and the levator palpebrae.
- Nuclei containing motoneurons innervating muscles derived from **branchial arches** (see Box 11-7):
 - The **motor trigeminal nucleus** contains motoneurons that control the muscles of mastication and one middle ear muscle, the tensor tympani.
 - The **facial nucleus** contains motoneurons that control muscles of facial expression and one middle ear muscle, the stapedius.
 - **Nucleus ambiguus** contains motoneurons that control muscles of the upper airway including those of the pharynx and larynx.
 - The upper cervical cord contains motoneurons whose axons enter the skull and then leave the skull as a cranial nerve to innervate two neck muscles, the sternocleidomastoid and the trapezius.
- Visceromotor nuclei contain preganglionic parasympathetic neurons that project to parasympathetic ganglia controlling autonomic functions of the head and body above the hindgut:
 - The **Edinger-Westphal nucleus** controls pupillary constriction and lens shape.
 - The **salivatory nuclei** control the production of tears, nasal secretions, and saliva.
 - The **dorsal motor nucleus of the vagus** provides parasympathetic control of the heart and other viscera and of the digestive tract above the hindgut.

In the previous chapter, the specific functions of each cranial nerve were detailed. In the next chapter on the anatomy of the brainstem, the cranial nerve nuclei will be more fully described.

BRANCHIAL ARCHES ARE DEVELOPMENTAL STRUCTURES THAT GIVE RISE TO SEVERAL OF THE MUSCLES IN THE HEAD.

In addition to somites, the head region of the vertebrate embryo contains collections of mesoderm called **pharyngeal** or **branchial arches**. In fish, branchial arches develop into the gills. In mammals, the branchial arches complement the somites as the source of bones, cartilage, and muscles in the head region. In the human, five arches give rise to the muscles of mastication, muscles of facial expression, middle ear muscles, most laryngeal muscles, the maxilla, and several cartilages in the upper airway. Muscles arising from branchial arches are termed *branchial muscles*, and the motoneurons that innervate them are *branchial motoneurons*.

INTERNAL BRAINSTEM ORGANIZATION FOLLOWS A MIDLINE-MOTOR TO LATERAL-SENSORY RULE

Remember that the spinal cord develops from a dorsally located alar plate, which gives rise to sensory neurons and a ventrally located basal plate giving rise to motor-related neurons (Fig. 11-7A). An indentation in the embryonic central canal, the sulcus limitans, marks the border between alar and basal plates and thus between dorsal sensory and ventral motor territories. Corresponding to the dorsal sensory and ventral motor gray areas, spinal roots carrying sensory information enter dorsally and roots carrying motor information into the periphery exit the spinal cord ventrally. The same sensory-motor separation principle holds in the hindbrain, but with a topographical relationship that runs from sensory functions laterally to motor functions medially. The sulcus limitans, still present as a shallow groove on the floor of the fourth ventricle (Fig. 11-2), remains the dividing point between sensory and motor territories.

Throughout the brainstem, the most medial pie slice contains somatic motoneurons (Fig. 11-7B). Lateral to this most medial region, but still medial to the sulcus limitans, visceromotor and branchial motoneurons reside. Pie slices lateral to the sulcus limitans contain sensory neurons, with visceral afferent and taste inputs arriving medially and somatosensory and special afferents more laterally. Thus, the brainstem contains slices that, from medial to lateral, are involved in:

- Somatomotor output to somatic muscles
- Output to parasympathetic ganglia and branchial muscles
- Receiving afferents from the viscera and from taste buds
- Receiving somatosensory and special afferents

Beyond this medial to lateral topography, neurons with different functions occupy different areas along the dorsal-ventral axis of each pie slice (Fig. 11-7B). Within the most medial pie slice, dedicated to innervating somatic muscles, motoneurons are all situated in the dorsal portion of the pie slice, close to both the midline and the ventricle. This principle even holds true outside of the hindbrain, in the midbrain, where motoneurons innervating five of the six extraocular muscles are located. In the second pie slice, preganglionic parasympathetic neurons are located dorsally, whereas those innervating branchial muscles collect in nuclei situated more ventrally.

Within the lateral sensory territory of the brainstem, the viscerosensory nucleus lies medial to the somatosensory nucleus, as would be expected from the transformation of the spinal ventral-to-dorsal topography into a brainstem medial-to-lateral one (Fig. 11-7B). Afferents from the special senses—hearing and balance—come into the sensory region lateral to the sulcus limitans but are restricted to the dorsal territory of the hindbrain. It is interesting to note that the inferior olives, the nuclei that make the olfactory tubercles, derive from the rhombic lip and occupy the ventromedial portion of the medulla.

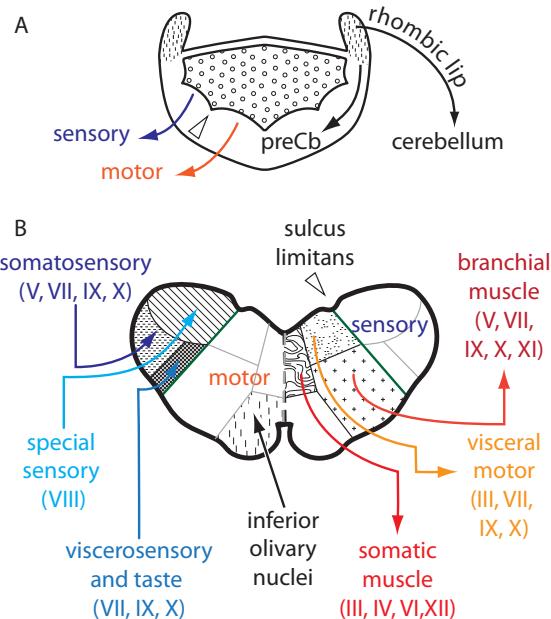


Figure 11-7. A: The same sensory-motor topography present in the developing spinal cord is present in the developing brainstem, but shifts due to the opening of the fourth ventricle. The pie slices devoted to each type of neuron are oriented from medial to lateral in the brainstem instead of from ventral to dorsal as in the spinal cord. B: In the adult brainstem, the organizational principles employ an imaginary diagonal line (green line on right) from the sulcus limitans to the ventrolateral surface of the brainstem. Nuclei medial to this line send axons out to serve motor functions and nuclei lateral to the line receive input from sensory afferents. Four slices encompassing the four functions of the spinal cord are represented, from medial to lateral: somatic motor, visceral motor, viscerosensory, and somatosensory. In addition to the medial-lateral organization, a dorsal-ventral organization is evident. Fit into this added dimension of organization are nuclei serving two functions not present in the spinal cord: branchial motor and special sensory input from inner ear. The branchial motor nuclei occupy the ventral portion of the pie slice containing visceromotor neurons. Neurons that receive special sensory input from inner ear afferents are located dorsally in a region spanning the two lateral pie slices. The organization illustrated here provides a rough guide as to the site where cranial nerves emerge from the brainstem. In the five cranial nerves with mixed functions, exit points are best predicted by the territory serving the nerve's primary function. For each functional territory the nerves that contain efferents from resident cranial nerve nuclei are listed. For example, cranial nerves III, IV, VI, and XII contain somatic motoneurons whose cell bodies are located in the somatic muscle region close to the midline. Finally, recall from Chapter 3 that cells that migrate from the rhombic lip during development form precerebellar nuclei, such as the inferior olfactory nuclei. Although most precerebellar nuclei are located in "motor" pie slices medial to the sulcus limitans, these nuclei do not send axons out of the central nervous system.

The pie-slice organization within the brainstem can aid the student trying to learn brainstem anatomy. Both the brainstem's internal structure and the exit points of the cranial nerves largely adhere to this organization, with only a few exceptions that will be discussed as they are encountered. By remembering, for example, that somatomotor neurons hug the midline, one can quickly narrow down the possible cranial nerve nuclei or cranial nerves present close to the midline. Learning to recognize the sulcus limitans in the floor of the fourth ventricle allows you to immediately deduce that structures medial of the sulcus limitans serve motor functions, whereas structures lateral to the sulcus limitans serve sensory functions.



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CHAPTER 12

INSIDE THE BRAINSTEM: CRANIAL NERVE NUCLEI AND LONG-DISTANCE CONNECTIONS

BRAINSTEM FUNCTIONS CHANGE FROM VEGETATIVE ONES CAUDALLY TO MORE EXPRESSIVE ONES ROSTRALLY

The brainstem divvies up the fundamental processes of human life, with the most automatic and basic ones supported most caudally. Progressively more complex, even luxurious, functions depend on more rostral brainstem regions. The functions of many neurons in the medulla, pons, and midbrain are associated with the functions of the cranial nerves that exit from each region. For example, the vagal nerve's exit from the medulla dictates the medulla's involvement in controlling blood pressure, gastrointestinal motility, and other homeostatic processes, whereas the midbrain's roles in vertical eye movements, vergence, and pupillary control follow from the oculomotor nerve's exit from the midbrain. Painting with a broad brush, neurons of the medulla, pons, and midbrain are largely responsible for different physiological processes:

- Medulla
 - Blood pressure
 - Breathing
 - Gastrointestinal motility

- Ingestion
- Equilibrium
- Pons
 - Conjugate horizontal eye movements (see Box 12-1)
 - Posture
 - **Rapid eye movement or REM sleep**
 - Facial expressions
- Midbrain
 - Vertical eye movements
 - Vergence (see Fig. 10-6D)
 - Pupillary control
 - Posture and locomotion
 - **Non-rapid eye movement or non-REM sleep**
 - Level of arousal

The above division of labor greatly oversimplifies the overlapping roles and multiple contributions of each brainstem region. For example, the medulla, pons, and midbrain all contribute to the maintenance of an upright posture against gravity. Yet, medullary lesions are most likely to disturb the sense of equilibrium, resulting in vertigo or disequilibrium, whereas midbrain lesions preferentially result in a person's adopting an abnormal posture. In addition to impairing normal functions (negative signs, see Box 1-1), damage to the brainstem also can give rise to a number of positive signs. For example, medullary damage can cause hiccups or nausea, the latter often associated with a disturbance of equilibrium.

Superimposed upon the different functions of nuclei in each brainstem region are the functions subserved by tracts traveling through them. Damage to any part of the

Box 12-1

CONJUGATE EYE MOVEMENTS OCCUR TOGETHER AS THOUGH THE TWO EYES WERE YOKED.

As introduced in Chapter 10, the positions of the two eyes must be coordinated, so that light from one location hits the same coordinates on the two retinas. When we shift our gaze from one location to another, the eyes move in conjugate, as though connected by a rigid yoke. For example, to look to a 1:00 position, we adduct and elevate our left eye while abducting and elevating our right eye to the same

degree. Although all vertical and torsional eye movements are conjugate, not all horizontal eye movements are conjugate. Vergence is part of the near triad for near vision and is a "normal" **disconjugate** eye movement. During vergence, both eyes adduct, and when switching from near to far vision, adduction is relaxed so that both eyes return to the neutral position.

brainstem can impair motor or sensory function by interrupting the corticospinal tract, medial lemniscus, spinothalamic tract, or any number of additional axonal highways that traverse the brainstem. In fact, Jean-Dominique Bauby, introduced in the first chapter, suffered from a pontine stroke that disrupted connections across the pons. In this chapter, we continue the caudal to rostral trip up the neuraxis that we began in Chapter 9. As we move from medulla to pons to midbrain, we note the locations of the three longest pathways, the cranial nerve nuclei, and of remarkable brainstem landmarks on selected cross-sections through the brainstem. The medulla contains the densest concentration of areas of interest and therefore we examine more medullary sections than pontine or midbrain ones.

THE SPINOMEDULLARY JUNCTION IS MARKED BY THE PYRAMIDAL DECUSSION

The first section that we examine is one that contains the pyramidal decussation (Fig. 12-1). This decussation, where the corticospinal tract crosses the midline, looks like a blurring of the midline from the outside (see Fig. 11-1), whereas in cross-section, the pyramidal decussation looks like an “x” with fibers from the right cerebral cortex crossing from the right pyramid to the left side and those from the left cerebral cortex crossing to the right. Just caudal to the pyramidal decussation, the crossing fibers reach their destination in the spinal dorsolateral funiculus, where they form the lateral corticospinal tract (see Fig. 9-8C).

The dorsal columns feed into the dorsal column nuclei starting at the spinomedullary junction and continuing more rostrally for several millimeters. Fibers in funiculus gracilis, carrying light touch, vibratory, and proprioceptive information from the legs and lower trunk terminate in nucleus gracilis. Fasciculus gracilis fibers, which populate the dorsal columns more caudally than fasciculus cuneatus fibers, also begin to terminate in the dorsal column nuclei more caudally than do fasciculus cuneatus fibers. At the level shown in Figure 12-1, the nucleus gracilis is capped dorsally by a minority of funiculus gracilis fibers that have not yet reached their destinations. In contrast, fasciculus cuneatus is large as only a small number of cuneatus fibers have terminated at or caudal to this level.

The spinothalamic tract, carrying pain and temperature information from the contralateral body, travels in the ventrolateral quadrant of the caudal medulla just as it did in the spinal cord.

As you recall from Chapter 10, the trigeminal nerve provides the bulk of the afferent input from the face and oral cavity. Trigeminal afferents enter the pons and their axons bifurcate or split to reach the **main or principal sensory nucleus** located in the pons (see below) and also to travel caudally in the **spinal trigeminal tract** (Fig. 12-2). Fibers in the spinal trigeminal tract terminate in the **spinal trigeminal nucleus**, which forms a long column that extends from the caudal pons through the full extent of the medulla. The most posterior part of the **spinal trigeminal nucleus**, the **pars caudalis**, is primarily concerned with pain and temperature from the face and oral cavity. Because this caudal portion of the spinal trigeminal nucleus receives

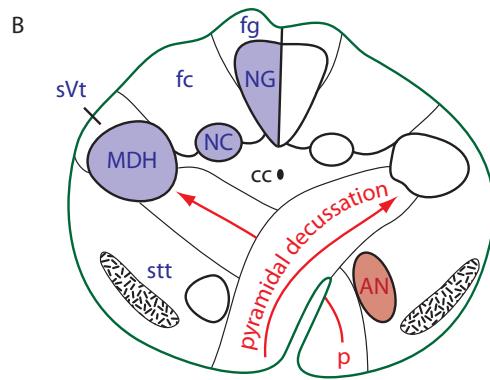
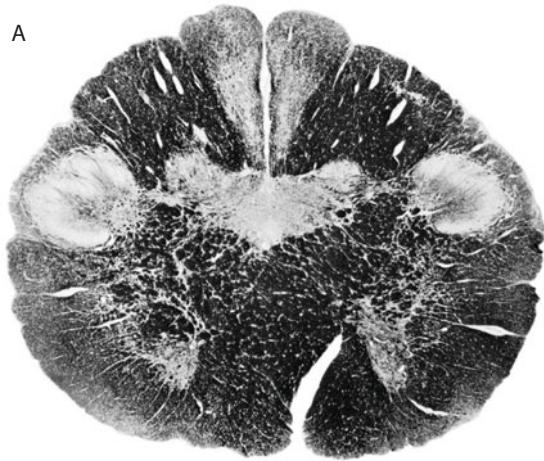


Figure 12-1. A photomicrograph (A) and diagram (B) of a section through the pyramidal decussation are shown. The photomicrograph in A and all others in this chapter have been stained so that myelin is black. As a consequence, white matter is black and gray matter is white in appearance. The spinomedullary junction is marked by the pyramidal decussation where corticospinal tract fibers traveling in the pyramids (*p*) cross the midline and travel dorsolaterally to travel in the lateral corticospinal tract. At this level, the fibers are still en route to the dorsolateral funiculus and so the lateral corticospinal tract is not yet formed. The pyramidal decussation is the motor decussation; above this level, the corticospinal pathway controls contralateral voluntary movements and below this level it controls ipsilateral voluntary movements. The spinothalamic tract (*stt*) is in roughly the same locale as in the spinal cord. At this level and throughout the brainstem, the spinothalamic tract carries pain and temperature information from the contralateral body. In this section, fibers from the dorsal columns have begun to terminate in the dorsal column nuclei. Many fibers from the fasciculus gracilis (*fg*) have terminated in nucleus gracilis (*NG*). As a consequence, the nucleus is large and the remaining fibers in the fasciculus gracilis are a minority. In contrast, only a small number of fibers in the fasciculus cuneatus (*fc*) have terminated in nucleus cuneatus (*NC*). Therefore, a large fasciculus cuneatus dominates a small nucleus cuneatus at this level. The fibers in the dorsal columns and the neurons in the dorsal column nuclei present in this section carry information about light touch, vibration, and proprioception from the ipsilateral body. The small solid circle in the center of the diagram in B represents the approximate location of the central canal (*cc*), which, although patent during embryogenesis, is occluded in the adult and therefore difficult to locate. The medullary dorsal horn (*MDH*), located dorsal and lateral to the central canal, is also called the *pars caudalis* of the spinal trigeminal nucleus. This portion of the spinal trigeminal nucleus receives primarily pain and temperature information from the ipsilateral face and oral cavity via the spinal trigeminal tract (*sVt*). The vast majority of the input to the medullary dorsal horn arises from the trigeminal nerve, with a minority of the input coming from cranial nerves VII, IX, and X. Motoneurons that innervate the sternocleidomastoid and trapezius muscles, muscles derived from branchial arches, originate in the ventral horn of the upper cervical cord, vestiges of which are present at this level. The cervical ventral horn containing sternocleidomastoid and trapezius motoneurons is sometimes referred to as the accessory nucleus (*AN*).

Photomicrograph reprinted and drawing modified with permission from deArmond S., et al. *Structure of the human brain: A photographic atlas*. New York: Oxford University Press, 1989.

mostly pain and temperature information, it is considered analogous to the superficial dorsal horn of the spinal cord. As is apparent in Figure 12-1, the caudal spinal trigeminal nucleus is easily recognized as it resembles the dorsal horn in appearance and is therefore often referred to as the **medullary dorsal horn**. Remember that the vagus, glossopharyngeal, and facial nerves innervate parts of the skin around the ear canal and ear. All somatic afferents from the face and mouth, regardless of their

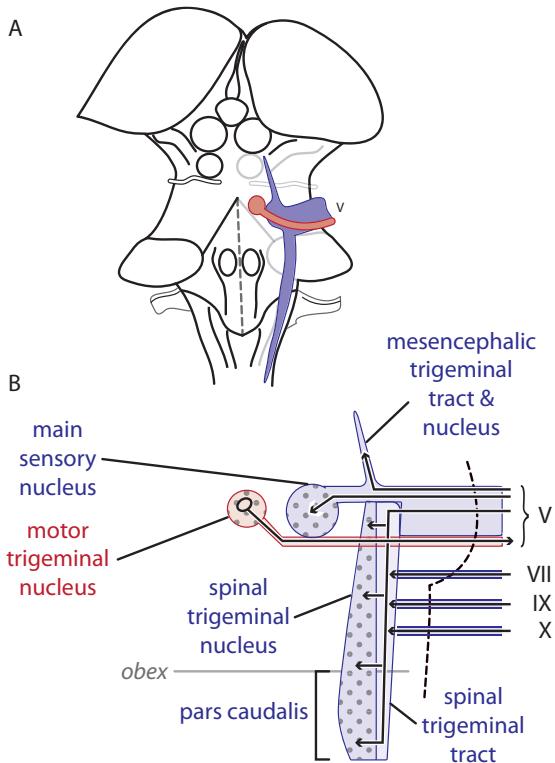


Figure 12-2. The central connections of the trigeminal nerve are diagrammed in anatomical relationship to brainstem landmarks (A) and in isolation (B). Panel A shows a cartoon of the dorsal view of an isolated brainstem. The trigeminal nerve consists of a large sensory root (blue) containing somatosensory information from the face, oral cavity, and nasopharynx, and a small motor root (red) containing the axons of motoneurons that innervate the muscles of mastication. The trigeminal sensory fibers enter the brainstem (dotted line in B) at the pons and terminate in three nuclei. First, trigeminal afferents that carry primarily tactile and vibratory information target the main sensory nucleus, located in the pons. Because it receives mostly low-threshold information, the main sensory nucleus is considered to be a rough trigeminal analog to the dorsal column nuclei. Second, trigeminal afferents descend in the spinal trigeminal tract to terminate in the long spinal trigeminal nucleus. The most caudal part of the spinal trigeminal nucleus, pars caudalis, is located caudal to the obex and receives mostly pain and temperature information. Thus, pars caudalis is considered to be a rough trigeminal analog to the superficial dorsal horn where spinal pain and temperature afferents terminate. Third, the axons of a small number of proprioceptive afferents travel in the mesencephalic trigeminal tract to terminate in the nucleus of the same name. The mesencephalic trigeminal nucleus is considered to be a trigeminal analog to Clarke's nucleus in the thoracic cord (see Fig. 9-9). Both process proprioceptive information and both project into the cerebellum. Since the mesencephalic trigeminal tract and nucleus are not involved in any common clinical syndromes, we do not consider these structures further. Somatosensory afferents from cranial nerves VII, IX, and X as well as V enter the spinal trigeminal tract and terminate in both the spinal trigeminal nucleus and the main sensory nucleus. The motor trigeminal nucleus is located in the pons, in a pie slice that is medial to the sulcus limitans. The motoneurons in the motor trigeminal nucleus innervate the muscles of mastication, such as the masseter and anterior digastric muscles, as well as one middle ear muscle, the tensor tympani. All the muscles innervated by the trigeminal nucleus are derived from branchial arches.

cranial nerve origin (V, VII, IX, X), terminate in the trigeminal nuclei, both spinal trigeminal nucleus and main sensory nucleus (Fig. 12-2).

A remnant of the spinal ventral horn combines with the medullary dorsal horn to give a section through the spinomedullary junction a decidedly spinal appearance (Fig. 12-1). Motoneurons in the cervical ventral horn and adjacent **accessory nucleus** of the caudal medulla innervate the sternocleidomastoid and the trapezius, two neck muscles derived from branchial arches (see Box 11-7) that are involved in head movements.

The major landmarks of the spinomedullary junction (Fig. 12-1) are listed in Box 12-2.

THE MOTOR DECUSSION MARKS THE SPINOMEDULLARY JUNCTION.

Landmarks related to major tracts:

Pyramidal decussation: corticospinal tract

Dorsal column nuclei (gracilis and cuneatus): dorsal column-medial lemniscus pathway carrying ipsilateral tactile, vibratory, and proprioceptive information

Spinothalamic tract: continues in ventrolateral quadrant, carrying contralateral pain and temperature information

Landmarks related to cranial nerves:

Accessory nucleus: branchial motor through XI

Spinal trigeminal nucleus, pars caudalis; or medullary dorsal horn: somatosensory from V, VII, IX, and X.

BETWEEN THE SPINOMEDULLARY JUNCTION AND THE OBEX, THE CAUDAL MEDULLA IS MARKED BY THE APPEARANCE OF THE INFERIOR OLIVES AND THE INTERNAL ARCUATE FIBERS

The medullary dorsal horn and remnants of the spinal ventral horn lend a spinal cord-like appearance to a cross-section at the level of the spinomedullary junction. However, cross-sections through the medulla rostral to the spinomedullary junction (see Figs. 12-3 to 12-6) do not resemble the spinal cord, giving rise to a “Toto, we’re not in Kansas anymore” feeling. Instead of the butterfly of gray matter surrounded by white matter that characterizes the spinal cord, the medulla contains interspersed nuclei and tracts. The nuclei and tracts mostly hug the outside of the brainstem, with the interior filled by a smattering of tracts, the occasional nucleus, and a region that looks like “filler,” the reticular formation. Recall from Chapter 11 that the reticular core of the brainstem serves fundamental, phylogenetically conserved homeostatic functions, such as the maintenance of blood pressure and regulation of breathing.

Ventrally, the pyramids appear as two triangularly shaped tracts on either side of the ventral midline, just where we would expect them to be from their external appearance (Fig. 12-3). Remember that the pyramids carry voluntary movement commands to muscles on the opposite side of the body. The spinothalamic tract, carrying pain and temperature from the contralateral body, remains located ventrolaterally.

The dorsal column nuclei are still present. At this level, very few gracilis fibers remain. The nucleus gracilis is waning in size while the nucleus cuneatus is large. The output from the dorsal column nuclei is clearly visible as gracefully arcing fibers (Fig. 12-3) called **internal arcuate fibers** that decussate to ascend contralaterally in the medial lemniscus destined for the somatosensory thalamus. This is the sensory decussation that was introduced in Chapter 9. Dorsal column nuclear neurons and internal arcuate fibers carry light touch, vibratory, and proprioceptive information from the ipsilateral side of the body. Just after crossing the midline and contralateral to the dorsal column nucleus from which they arose, axons take a 90-degree turn to travel rostrally as the medial lemniscus. The medial lemnisci straddle the midline region just dorsal to the pyramids, with the right medial lemniscus carrying sensory information from the left side of the body and the left medial lemniscus carrying sensory information from the right side of the body (see Box 12-3).

In the section through the caudal medulla represented in Figure 12-3, several cranial nerve nuclei are apparent. The medullary dorsal horn, first seen at the level of the spinomedullary junction, is still present. The medullary dorsal horn receives mostly pain and temperature input, as well as some tactile input, from the ipsilateral mouth and face.

The locations of nuclei in the central gray with respect to the imagined center of the central gray, the site of the central canal, are useful clues as to nuclear

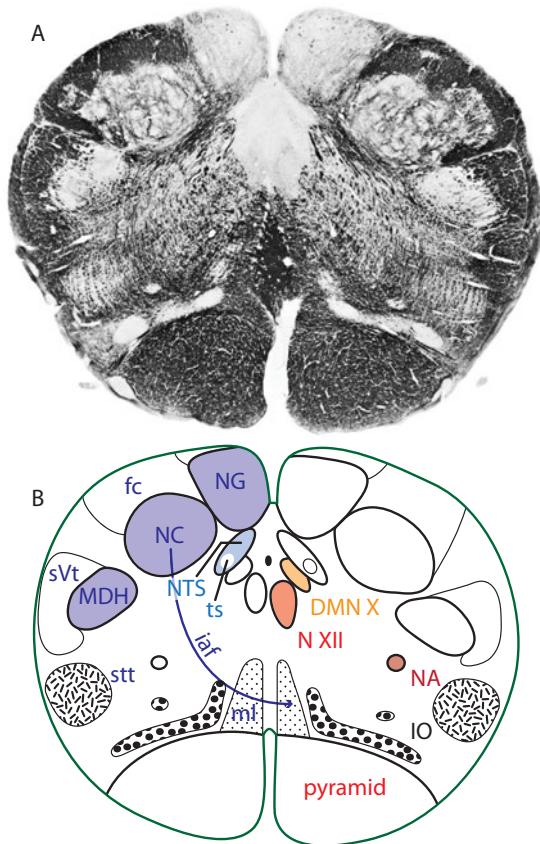


Figure 12-3. A photomicrograph (A) and diagram (B) of a section through the caudal pole of the sensory decussation are shown. At this level, rostral to the pyramidal decussation, the corticospinal pathways travel in the pyramids. Each pyramid carries fibers that influence voluntary movement of muscles on the contralateral side. The spinothalamic tract, carrying pain and temperature information from the contralateral body, is still traveling in the ventrolateral quadrant. Virtually all of the fibers from the fasciculus gracilis have terminated in nucleus gracilis (NG) at or caudal to this level. Only a very small remnant of the fasciculus gracilis (unlabeled) is present capping the nucleus. Many but not all of the fibers in the fasciculus cuneatus (fc) have terminated in nucleus cuneatus (NC), which is more sizeable at this level than at the spinomedullary junction. Recall that neurons in the dorsal column nuclei project to the thalamus through the medial lemniscus (ml). The sensory decussation refers to axons from dorsal column nuclear neurons that arc around and cross the midline as internal arcuate fibers (iaf). The internal arcuate fibers can be clearly seen in the photomicrograph at top, and one arcuate trajectory is represented in the diagram at the bottom. Both the neurons in the dorsal column nuclei and the internal arcuate fibers carry information about light touch, vibration, and proprioception from the ipsilateral body. The same axon that is called an internal arcuate fiber prior to crossing the midline is part of the medial lemniscus after crossing the midline. Due to the decussation, medial lemniscus axons carry light touch, vibration, and proprioception from the *contralateral* body. Somatosensory fibers from cranial nerves V, VII, IX, and X travel in the spinal trigeminal tract (sVt) to reach the medullary dorsal horn (MDH). At this level, most of the somatosensory input to the medullary dorsal horn concerns pain and temperature from the ipsilateral face and oral cavity. Additional cranial nerve nuclei are present as well. The nucleus of the solitary tract or nucleus tractus solitarius (NTS) surrounds the solitary tract or tractus solitarius (ts). The tractus solitarius contains primary afferents from cranial nerves VII, IX, and X, which carry viscerosensory information into the nucleus. Ventral to the nucleus of the solitary tract are three motor nuclei. The dorsal motor nucleus of the vagus (DMN X) contains preganglionic parasympathetic neurons that exit through the vagus nerve to innervate ganglia in the body's viscera above the hindgut. The nucleus ambiguus (NA) contains motoneurons that innervate the branchial arch-derived skeletal muscles of the upper airway. Nucleus ambiguus is so named because its borders are difficult to discern in sections prepared with most stains, including myelin stains. Ambiguus motoneurons project through both glossopharyngeal and vagal nerves to laryngeal and pharyngeal muscles critical to swallowing and speech. The hypoglossal nucleus (N XII) contains motoneurons that send axons through the hypoglossal nerve to innervate the various glossus muscles of the tongue. The caudal beginnings of the large medullary precerebellar complex of inferior olivary (IO) nuclei (regions with dots) are present in this section. Although each cluster of cells constitutes a separate inferior olivary nucleus with a separate name, it is sufficient to refer to the conglomeration of nuclei as the inferior olivary complex or simply as the inferior olive (IO).

Photomicrograph reprinted and drawing modified with permission from deArmond S., et al. *Structure of the human brain: A photographic atlas*. New York: Oxford University Press, 1989.

Box 12-3

THE PATTERN OF A SENSORY DEFICIT CAN REVEAL THE LOCATION OF A LESION.

Just as loss of pain and temperature sensation on one side and of tactile sensation on the opposite side implies a spinal lesion, loss of all sensation on one side of the face and from the opposite side of the body points to a brainstem lesion. This is because, rostral to the dorsal column nuclei, both the medial lemniscus and the spinothalamic tract carry information about the contralateral side of the body, whereas sensory trigeminal tracts carry somatosensory information from the ipsilateral face and oral cavity. Within the forebrain, sensory tracts carry information about the contralateral face and body. Thus, by mapping out sensory deficits, one can quickly narrow down the most likely location of a lesion as shown in Table 12-1.

function. Thus, the **hypoglossal nuclei**, containing somatic motoneurons, appear as two discrete ovals located ventrally and medially, just off the midline (Figs. 12-3). The hypoglossal nuclei contain the motoneurons that innervate tongue muscles via the hypoglossal nerve. Lateral, and a bit dorsal to the hypoglossal nucleus is the **dorsal motor nucleus of the vagus**, a visceromotor nucleus. The dorsal motor nucleus of the vagus contains preganglionic parasympathetic motor neurons that influence the function of thoracic and abdominal viscera above the hindgut via the vagus nerve's projections to parasympathetic ganglia. A third motor nucleus, **nucleus ambiguus**, contains motoneurons that innervate the upper airway muscles. Since the upper airway muscles are derived from branchial arches rather than somites, nucleus ambiguus is a branchial motor nucleus. Accordingly, it is located ventrally within the pie slice that also contains the dorsal motor nucleus of the vagus more dorsally.

Lateral and dorsal to the motor nuclei, visceral afferents travel in a tight bundle of myelinated axons called the **tractus solitarius**, or **solitary tract**. The afferents in the solitary tract terminate in the gray matter immediately surrounding the solitary tract, the **nucleus of the solitary tract** or **nucleus tractus solitarius**, often abbreviated as **NTS**. The solitary tract is an island of white matter located fully within the bounds of the nucleus tractus solitarius. Sensory visceral information from the thoracic and abdominal viscera, larynx, pharynx, trachea, and esophagus, carried in the vagus and glossopharyngeal nerves, travels in the solitary tract and terminates in the caudal part of the nucleus of the solitary tract. Input from taste buds in the tongue, palate, and upper airway also travels in the solitary tract more rostrally and terminates in the rostral part of the nucleus of the solitary tract (see more on this below).

Ventrally, a distinctive nucleus that marks the caudal medulla makes its first appearance. This is the inferior olive, the nuclei under the bump that is the olivary tubercle (see Chapter 11) and the source of a very important input to the cerebellum, cerebellar afferents called **climbing fibers**. Although not directly related to any cranial nerve or to any of the three long tracts, the inferior olives warrant our attention as they are so distinctive that they provide an easy way to recognize a medullary section.

TABLE 12-1. THE REGIONS WITH A SOMATOSENSORY LOSS ARE LISTED FOR LESIONS AT THREE DIFFERENT LEVELS IN THE NEURAXIS

SITE OF LESION	TACTILE INPUT FROM THE BODY	PAIN AND TEMPERATURE INPUT FROM THE BODY	SENSORY INPUT FROM THE FACE
Spinal	Ipsilateral dermatomes at and below the lesion	Contralateral dermatomes at and below the lesion	Not affected
Brainstem (rostral to the sensory decussation)	Contralateral body	Contralateral body	Ipsilateral face
Forebrain	Contralateral body	Contralateral body	Contralateral face

THE CAUDAL MEDULLA IS DENSELY POPULATED BY CRANIAL NERVE NUCLEI

As we move rostrally in the medulla (Fig. 12-4), the same regions introduced in Figure 12-3 are present. Yet, this section features three structures—nucleus cuneatus, the internal arcuate fibers, and the inferior olive—more prominently than did the previous section. Here, we briefly review the long pathways, cranial nerve nuclei, and other remarkable medullary landmarks.

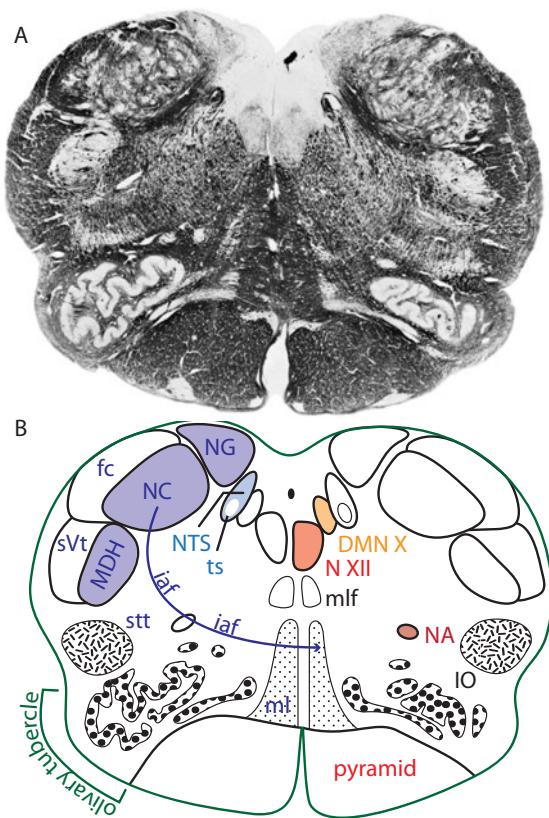
The pyramids and spinothalamic tract remain in the same positions that they occupied in the previous section. The dorsal column nuclei are more fully developed. No fibers remain in fasciculus gracilis, and the nucleus gracilis is waning in size. Nucleus cuneatus is now well formed. In addition, internal arcuate fibers from both dorsal column nuclei crowd the central portion of this section.

The same cranial nerve nuclei that were present in the last section are still present. The medullary dorsal horn is diminished in size but still visible. The hypoglossal nucleus, dorsal motor nucleus of the vagus, nucleus ambiguus, and nucleus tractus solitarius all remain in the same locations as they were in the previous section.

The inferior olives are more elaborated in this section. The inferior olives are actually a complex of multiple nuclei, more of which are present in the section illustrated in Figure 12-4 than that in Figure 12-3. Because of the larger inferior olivary territory, a noticeable bulge, the olivary tubercle, is noticeable.

Figure 12-4. A photomicrograph (A) and diagram (B) of a section through the rostral sensory decussation are shown. The structures present at this level are similar to those in Figure 12-3 and will be described only briefly. As is now familiar, the corticospinal pathways travel in the pyramids, and the spinothalamic tract (stt) travels in the ventrolateral quadrant. Nucleus cuneatus (NC) and the rostral pole of nucleus gracilis (NG) are distinctive in this section. A minority of fasciculus cuneatus (fc) remains; these fibers are destined to terminate just a bit rostrally. Internal arcuate fibers (iaf) continue to leave the dorsal column nuclei and trace an arcing path into the medial lemniscus. Medial lemniscus axons carry light touch, vibration, and proprioception from the *contralateral* body. The medial longitudinal fasciculus (mlf), a tract involved in gaze coordination, straddles the midline just ventral to the hypoglossal nuclei. Three cranial motor nuclei—the hypoglossal nuclei (N XII), dorsal motor nuclei of the vagus (DMN X), and nuclei ambiguus (NA)—are present in this section. Two sensory nuclei and associated tracts are also present: the rostral pole of the medullary dorsal horn (MDH), spinal trigeminal tract (sVt), nucleus tractus solitarius (NTS), and solitary tract (ts). The inferior olivary complex is larger and more elaborate in this section and forms a small bulge in the ventrolateral medulla. This bulge is the olivary tubercle (see *et al.* in Fig. 11-4A).

Photomicrograph reprinted and drawing modified with permission from deArmond S., et al. *Structure of the human brain: A photographic atlas*. New York: Oxford University Press, 1989.



One new feature makes its appearance in the section illustrated in Figure 12-4. The **medial longitudinal fasciculus**, a tract that runs between the upper cervical cord and the midbrain, and coordinates conjugate eye and head movements (see Chapter 26) can be seen in this section. As the medial longitudinal fasciculus, often referred to as the **MLF**, is easily distinguished, it is a valuable navigational landmark, particularly in more anterior sections.

The major landmarks of the caudal medulla (Figs. 12-3, 12-4) are reviewed in Box 12-4.

CRANIAL NERVE ROOTLETS AND THE OPENING OF THE FOURTH VENTRICLE MARK THE MID-MEDULLA

Progressing rostrally, the most remarkable transformation present in the mid-medulla, but not in the caudal medulla, is the opening of the fourth ventricle (Fig. 12-5). The floor of the fourth ventricle forms the dorsal border of the

Box 12-4

NUCLEI CRITICAL TO FUNDAMENTAL PHYSIOLOGICAL PROCESSES ARE FOUND IN THE CAUDAL MEDULLA.

Landmarks related to major tracts:

Pyramids: corticospinal tract carrying the commands for voluntary movement destined for the contralateral side of the body

Dorsal column nuclei (gracilis and cuneatus): dorsal column nuclear neurons send out axons that approach the midline as internal arcuate fibers and then turn rostrally to form the medial lemniscus. This is the caudal pole of the sensory decussation.

Medial lemniscus: straddles the midline above the pyramids and carries contralateral tactile and vibratory information

Spinothalamic tract: continues in ventrolateral quadrant, carrying contralateral pain and temperature information

Landmarks related to cranial nerves:

Hypoglossal nucleus: somatomotor through XII

Dorsal motor nucleus of the vagus: visceromotor through IX and X

Nucleus ambiguus: branchial motor to upper airway muscles (IX, X)

Nucleus of the solitary tract: viscerosensory from X and IX and taste from VII (rostral two-thirds of the tongue), IX (caudal third of the tongue and soft palate), and X (uvula and pharynx)

Spinal trigeminal nucleus, pars caudalis; or medullary dorsal horn: somatosensory from V, VII, IX, and X

Additional notable landmarks:

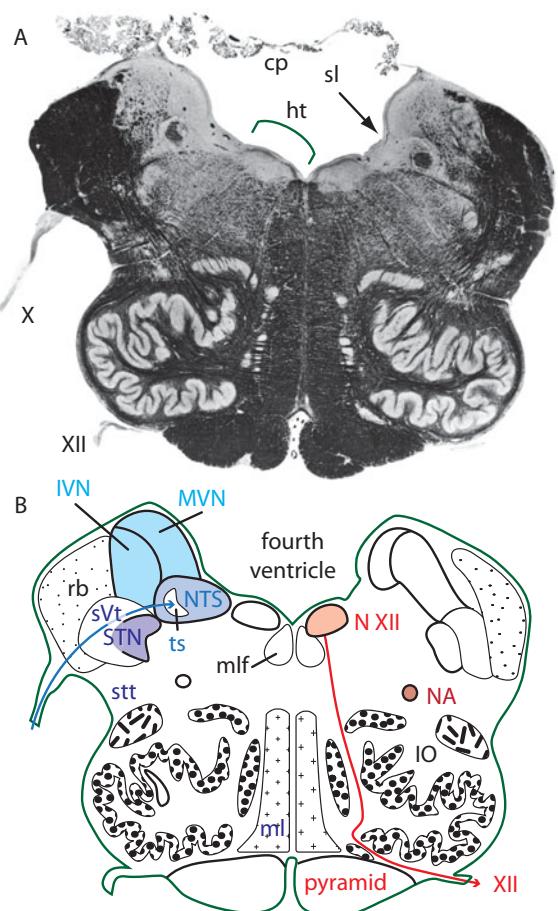
Inferior olive: sends climbing fibers into the cerebellum

Medial longitudinal fasciculus: carries axons critical to coordination of eye and head movements

Reticular formation: fills the core with neurons and axons important to fundamental body processes, such as regulation of breathing and blood pressure.

Figure 12-5. A photomicrograph (A) and diagram (B) of a section through the mid-medulla are shown. The fourth ventricle has opened up and choroid plexus (cp in A) is visible. The pyramids, spinothalamic tract (stt), and medial lemniscus (ml) are in familiar locations. The elaborate inferior olives (IO) continue to bulge out underlying the olfactory tubercles. The medial longitudinal fasciculus (mlf) straddles the dorsal midline. Motor cranial nerve nuclei are present in pie slices medial to the sulcus limitans (sl in A), and sensory cranial nerve nuclei are present laterally. The hypoglossal nucleus (N XII) is still present and in fact forms a small bump, the **hypoglossal trigone** (ht in A), in the floor of the fourth ventricle. Hypoglossal motoneurons send their axons ventrally and then laterally to exit the medulla (rootlet labeled XII in A and red line in B). The rostral pole of the nucleus ambiguus (NA) is present, ventral to the hypoglossal nucleus and just dorsal to the inferior olives. The spinal trigeminal nucleus (STN) and spinal trigeminal tract (sVt) are diminished in size and less prominent at this level compared to levels caudal to the obex (see Figs. 12-1, 3, and 4). Two vestibular nuclei make their first appearance in this section. The medial vestibular nucleus (MVN) is a homogenous looking region located just lateral to the sulcus limitans. The inferior vestibular nucleus (IVN) is located lateral to the medial vestibular nucleus and has a distinctive checkerboard appearance. The restiform body (rb), located in the dorsolateral medulla, contains spinocerebellar fibers carrying somatosensory, proprioceptive, and viscerosensory information, which are destined to enter the cerebellum through the inferior cerebellar peduncle.

Photomicrograph reprinted and drawing modified with permission from deArmond S., et al. *Structure of the human brain: A photographic atlas*. New York: Oxford University Press, 1989.



medulla at this level. The caudal region of the fourth ventricle houses the choroid plexus, which looks like irregular “crud” floating in the ventricle. The choroid plexus in the roof of the fourth ventricle, along with that present in the third and lateral ventricles, produces cerebrospinal fluid (see Chapter 14). Visible on the floor of the fourth ventricle is the sulcus limitans, the indentation that marks the boundary between sensory and motor nuclei related to cranial nerves. Although not attached to the medulla, the cerebellum is located above the medulla and fourth ventricle at this level.

The mid-medulla (Fig. 12-5) contains most of the same regions present more caudally (Fig. 12-4). Consequently, several structures may look familiar:

- The pyramids carrying messages for voluntary movement of contralateral muscles run the length of the medulla.
- The medial lemniscus carrying tactile, vibratory, and proprioceptive information from the contralateral body is in the same medial location, sandwiched between the inferior olives, and is still oriented in a dorsal-ventral direction. The dorsal column nuclei are notably absent.
- The spinothalamic tract still travels ventrolaterally, carrying pain and temperature information from the contralateral body.
- The inferior olives are large and elaborate at this level, bulging out to form the olfactory tubercle.

- The medial longitudinal fasciculus, important in coordinating eye and head movements, is still present as a discrete bundle of axons.

Five nuclei related to cranial nerves that were present more caudally, and one additional cranial nerve nucleus, are visible. From medial to lateral, and thus motor to sensory, they are:

- The hypoglossal nucleus contains motoneurons that control tongue musculature.
- The dorsal motor nucleus of the vagus contains autonomic motor neurons bound for parasympathetic ganglia of the viscera above the hindgut.
- Nucleus ambiguus containing motoneurons that innervate muscles of the upper airway remains situated ventrally within the medullary reticular formation.
- The nucleus of the solitary tract and the solitary tract are clearly visible. At this level, the nucleus of the solitary tract is devoted to processing taste input from cranial nerves VII, IX, and X.
- Two of the four **vestibular nuclei**, all of which process input from the labyrinth related to head position and movement, appear in the mid-medulla (see more below).
- The spinal trigeminal tract carries somatosensory input from the face and oral cavity to a far less distinctive part of the spinal trigeminal nucleus than was present in more caudal sections.

Two vestibular nuclei, present at more caudal medullary levels, become more prominent in the mid-medulla. Vestibular afferents are excited by head acceleration, including that caused by Earth's gravity. They enter at the pontomedullary junction as the vestibular component of cranial nerve VIII and project to one or more of the four vestibular nuclei. The two vestibular nuclei present within the mid-medulla are important in keeping gaze steady through control of eye and head movements and in keeping an upright posture against the force of gravity.

A few additional structures demand our attention. The section in Figure 12-5 contains hypoglossal and vagus nerve roots (Fig. 12-5A). The hypoglossal nerve emerges between the lateral edge of the pyramid and the medial edge of the olive. In cross-section, one sees well myelinated (and therefore darkly stained in myelin-stained tissue) hypoglossal axons travel ventrally from the hypoglossal nucleus and then turn laterally at a point ventral to the inferior olives to emerge from the medullary ventrum. Vagal roots enter the medulla more laterally. Vagal axons travel dorsomedially to reach the nucleus of the solitary tract and the dorsal motor nucleus of the vagus. Just a bit more rostrally, glossopharyngeal nerve roots emerge from the same area as do the vagus nerve roots in this section (see Box 12-5).

The final structure that we recognize here is the **restiform body**, a tract that carries somatosensory and proprioceptive information from the spinal cord, as well as climbing fibers from the inferior olive into the cerebellum. The axons of inferior olive neurons cross the midline, course through the contralateral inferior olive,

Box 12-5

NO CLEAR BOUNDARY DIVIDES VAGAL FROM GLOSSOPHARYNGEAL ROOTLETS.

Only very small, pin-point traumatic injuries would affect either the vagus or glossopharyngeal nerve rootlets without affecting the other. Therefore, it is rarely important to make the difficult determination whether any given fascicle emerging from the lateral medulla joins the vagus or the glossopharyngeal nerve.

and then arc into the restiform body. Moving rostrally through the medulla, the progressively larger restiform body foreshadows the appearance of the cerebellar peduncles into which it feeds. Ultimately, climbing fibers as well as axons from three spinocerebellar tracts enter the cerebellum through the restiform body. Because of the importance of the information carried in the restiform body to proper cerebellar function, injury to the restiform body results in ataxia (see Fig. 11-5) just as injury to the cerebellum itself does.

The major landmarks of the mid-medulla (Fig. 12-5) are listed in Box 12-6. Lateral structures in the mid- and caudal medulla are impaired in Wallenberg syndrome (see Box 12-7).

IN THE ROSTRAL MEDULLA, THE FACIAL AND COCHLEAR NUCLEI APPEAR AS NUCLEI RELATED TO VISCERAL FUNCTION FADE

Several now-familiar structures listed above are still present in the rostral medulla (Fig. 12-6). The pyramids occupy the base of the section. The medial lemniscus stands vertically between the large and elaborate inferior olives. The spinothalamic tract remains in the ventrolateral portion of the medulla. Other familiar landmarks still present are the medial longitudinal fasciculus and

Box 12-6

THE FOURTH VENTRICLE OPENS UP IN THE MID-MEDULLA.

Landmarks related to major tracts:

Pyramids: corticospinal tract carrying the commands for voluntary movement destined for the contralateral side of the body

Medial lemniscus: carrying tactile, vibratory, and proprioceptive information from the contralateral body

Spinothalamic tract: carrying pain and temperature information from the contralateral body

Landmarks related to cranial nerves:

Hypoglossal nucleus: somatomotor to tongue muscles through XII

Nucleus ambiguus: branchial motor to upper airway muscles (IX, X)

Nucleus of the solitary tract: viscerosensory from X and taste from VII (rostral two-thirds

of the tongue), IX (caudal third of the tongue and soft palate), and X (uvula and pharynx)

Vestibular nuclei: special sensory from VIII

Spinal trigeminal nucleus: somatosensory from V, VII, IX, and X

Additional notable landmarks:

Inferior olive: sends climbing fibers into the cerebellum

Medial longitudinal fasciculus: carries axons critical to coordination of eye and head movements

Reticular formation: fills the core with neurons and axons important to fundamental body processes such as ingestion

Restiform body: carries spinal and inferior olivary input to the cerebellum.

PATIENTS WITH WALLENBERG SYNDROME HAVE DEFICITS IN FUNCTIONS THAT DEPEND ON THE LATERAL MEDULLA.

Blockage of an artery supplying the lateral medulla causes **Wallenberg** or **lateral medullary syndrome**. Patients with Wallenberg syndrome have impaired functioning of the caudal spinal trigeminal nucleus, spinothalamic tract, nucleus ambiguus, nucleus of the solitary tract, vestibular nuclei, and restiform body. Common symptoms of Wallenberg syndrome include:

- Ipsilateral anesthesia, or loss of sensation, in the face and oral cavity is due to damage to the caudal spinal trigeminal tract and nucleus. The most dangerous element of this symptom is the loss of corneal sensation and associated absence of the protective blink reflex. Corneal scarring can result if irritants are not blinked away.
- Impaired pain and temperature sensation on the contralateral side of the body results from damage of the spinothalamic tract.
- Dysphagia, impairment of swallowing, and dysarthria, impairment of speech articulation, occur because of damage to nucleus ambiguus.

- Damage to the nucleus of the solitary tract causes a loss of taste sensation on the ipsilateral tongue.
- Vertigo and nausea, abnormal eye movements, and ataxia (see Fig. 11-5) are consequences of damage to the vestibular nuclei and restiform body.
- Horner syndrome (see Box 9-3), consisting of miosis, or pupillary constriction, and ptosis, or drooping eyelid, develops because a tonic excitatory input to sympathetic neurons in the thoracic cord is interrupted. This excitatory input travels near the spinothalamic tract and is typically lesioned in Wallenberg syndrome.

The symptoms of the lateral medullary syndrome encapsulate a large number of medullary functions. Absent from the syndrome are problems with voluntary movements, since the corticospinal tract travels so close to the midline of the medulla. Also typically absent are symptoms related to somatomotor and visceromotor functions of medial medullary nuclei: the hypoglossal nucleus and the dorsal motor nucleus of the vagus.

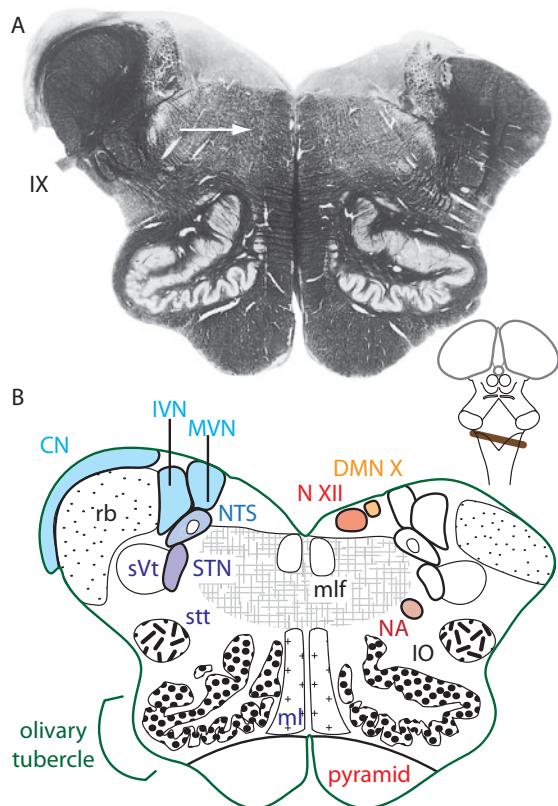
restiform body. The medullary reticular formation plays important roles in the regulation of heart rate, blood pressure, breathing, and ingestion.

Nucleus ambiguus, the dorsal motor nucleus of the vagus and the hypoglossal nuclei, cranial nerve nuclei related to the glossopharyngeal, vagus, and hypoglossal nerves, are not present in the rostral medulla. The rostral pole of the nucleus of the solitary tract, a region concerned with processing taste input, is present. Near the nucleus of the solitary tract at this level is the **inferior salivatory nucleus** containing motoneurons that project to the parotid gland involved in saliva production. The inferior salivatory nucleus is neither large nor distinct enough to allow easy identification; the reader should simply remember that such neurons are present at this level within the reticular core. The caudal vestibular nuclei are still present, as is the spinal trigeminal nucleus and associated tract. Roots of the glossopharyngeal nerve emerge from the dorsolateral surface of the rostral medulla.

The hearing-related **cochlear nuclei**, which receive all auditory input from the cochlea, form an outer cap on the restiform body. They appear in the rostral medulla in anticipation of the pontomedullary junction where the vestibulocochlear

Figure 12-6. A photomicrograph (A) and diagram (B) of a section through the rostral medulla are shown. Sections are often cut obliquely as is the case for this section. The left half of this section is from a more rostral level than is the right half of the section; the heavy brown line in the inset shows the approximate plane of section. As we are interested in the rostral medulla, we focus on the left half of the section. The right half of the section contains mid-medullary structures as described in the caption for Figure 12-5. The pyramids, medial lemniscus (*m*), and spinothalamic tract (*stt*) remain in the same relative locations as in previous sections. The inferior olives (*IO*) remain conspicuous medullary markers. The medial longitudinal fasciculi (*mlf*) remain as a pair of distinct tracts straddling the dorsal midline. The restiform body (*rb*) has swelled with more fibers en route to the cerebellum. In the rostral medulla (the left half of the section), the hypoglossal nucleus is no longer present, and in fact, there is no motor cranial nerve nucleus at this level. The central core of the medulla is occupied by reticular formation (white arrow in A and hatching in B). Lateral to the motor region are the medial (MVN) and inferior (IVN) vestibular nuclei. The checkerboard appearance of the inferior vestibular nucleus is formed by interspersed cells (unstained and therefore white) and myelinated axons (stained and therefore black) entering from the nerve root. The cochlear component of cranial nerve VIII projects into the cochlear nuclei (CN), which cap the restiform body. The inferior salivatory nucleus (not labeled) provides input to parasympathetic neurons in the otic ganglion that control salivation from the parotid gland. The inferior salivatory nucleus is an indistinct cluster of cells within the medullary reticular formation that borders the rostral pole of the nucleus of the solitary tract (NTS) where taste is processed.

Photomicrograph reprinted with permission from Bruni, J.E., and Montemurro, D. *Human neuroanatomy: A text, brain atlas, and laboratory dissection guide*. New York: Oxford University Press, 2009.



nerve enters. Although the cochlear nuclei receive **monaural** input, or input from a single ear, the ventral cochlear nucleus projects bilaterally to downstream auditory nuclei (Fig. 12-7). Therefore, *auditory pathways beyond the cochlear nuclei receive information about sound arriving at both ears*. Because of this early bilateralization of auditory information, the left and right sides of the brain process input from both the left and right ears. For this reason, traumatic injuries that render a person deaf do so by injuring the cochlea, the vestibulocochlear nerve, or a cochlear nucleus, whereas injuries to central auditory pathways do not cause deficits in hearing as a rule.

The landmarks of the rostral medulla are listed in Box 12-8.

THE BASIS PONTIS AND THE MIDDLE CEREBELLAR PEDUNCLES MARK THE PONS

Because of its position midway between the spinal cord and cerebral cortex and its role as a requisite way-station for cerebral input to the cerebellum, the pons is like an air traffic hub, housing massive numbers of axons en route elsewhere, along with a local neuronal population large enough to provide support. The transition from medulla to pons is marked, without any trace of subtlety, by the

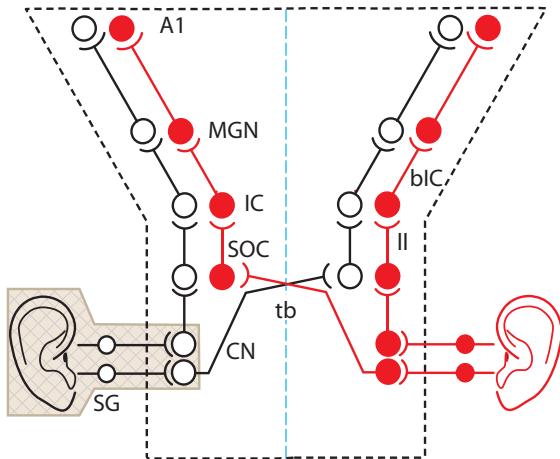


Figure 12-7. Information from the left ear (black) arrives in the left cochlear nucleus, and input from the right ear (red) reaches the right cochlear nucleus. Cochlear nuclear neurons project to auditory nuclei on both ipsilateral and contralateral sides. Therefore, auditory pathways beyond the cochlear nuclei contain information about sounds arriving at both ears. For this reason, we largely skip over auditory tracts in this textbook except to briefly diagram them here. Cochlear nuclear neurons project to both the ipsilateral and the contralateral **superior olfactory complex (SOC)**. The projection from the cochlear nucleus to the contralateral superior olfactory complex travels across the midline (blue dashed line) in the **trapezoid body (tb)**. Neurons in the superior olives project through the **lateral lemniscus (II)** to the **inferior colliculus (IC)**. Cells in the inferior colliculus travel through the brachium of the inferior colliculus (**bIC**) to the medial geniculate nucleus (**MGN**). Neurons in the medial geniculate nucleus in turn project to auditory cortex (**A1**). Since auditory information from both ears is present on both sides of the brain (black dashed line), a **unilateral central lesion above the cochlear nuclei cannot produce deafness**. Therefore, hearing problems are caused by damage to the ear, the spiral ganglion (**SG**), cranial nerve VIII (not labeled), or the cochlear nucleus (tan hatched region).

appearance of the massive middle cerebellar peduncles and the basis pontis (Fig. 12-8). The middle cerebellar peduncle forms the bulk of the attachment of the cerebellum to the brainstem as well as the lateral walls of the fourth ventricle. The superior cerebellar peduncles, visible in the dorsolateral roof of the fourth ventricle, carry the output of the cerebellum destined for midbrain and forebrain.

Box 12-8

THE COCHLEAR NUCLEI MARK THE ROSTRAL MEDULLA.

Landmarks related to major tracts:

Pyramids: carrying commands for voluntary movement of the contralateral body

Medial lemniscus: carrying low-threshold information from the contralateral body

Spinothalamic tract: carrying pain and temperature information from the contralateral body

Nuclei related to cranial nerves:

Nucleus of the solitary tract: taste from VII (rostral two-thirds of the tongue), IX (caudal third of the tongue and soft palate), and X (uvula and pharynx)

Spinal trigeminal nucleus: processes somatosensory input from face and mouth

Vestibular nuclei: process balance

Cochlear nuclei: process auditory input

Additional notable landmarks:

Inferior olive: source of climbing fibers, a critical input to the cerebellum

Medial longitudinal fasciculus: carrying axons critical to orienting head and eye movements

Reticular formation: fills the core with neurons and axons important to fundamental body processes such as salivation and ingestion

Restiform body: carrying spinal and inferior olfactory input to the cerebellum.

At the pontomedullary junction, the medullary pyramids enter the basis pontis (Fig. 12-8). Just as pyramids define the medulla, the basis pontis denotes pontine territory. The basis pontis contains three components:

- Neurons of the pontine nuclei, which are the resident cells of the basis pontis
- Axons of pontine neurons, which cross the midline and enter the middle cerebellar peduncle; once in the cerebellum, these axons are known as **mossy fibers**
- Corticospinal fibers en route from the cerebral cortex to the spinal cord with information related to voluntary movements of contralateral muscles.

Corticospinal fibers, en route from the ipsilateral cerebral cortex to the contralateral spinal cord, are cut transversely and appear “on end” in a transverse section (circled x in Fig. 12-8A). As they pass through the pons, many corticospinal fibers give off collaterals that contact neurons in the pontine nuclei. Fibers that descend from cortex to reach pontine nuclear neurons either exclusively or as collaterals comprise a **corticopontine tract**. Pontine nuclear neurons, in turn, send a projection across the midline and through the middle cerebellar peduncle into the cerebellum. As the axon of a pontine nuclear cell crosses the pons, it is cut longitudinally (white arrowhead in Fig. 11-8A). Pontine nuclear axons carry information about intended movements similar to the information that is sent to the spinal cord via the corticospinal tract.

The dorsal half of the pons contains the **pontine tegmentum** populated by cranial nerve-related structures, long tracts, and reticular formation (Fig. 12-8B). Within the tegmentum are found the medial lemniscus and spinothalamic tract, both of which have shifted in orientation relative to medullary levels. The medial lemniscus stretches diagonally from a slightly dorsal position next to the midline to a more ventral position laterally (Fig. 12-8C). The medial lemniscus carries tactile, vibratory, and proprioceptive information from the contralateral legs, trunk, and arms. Lateral to the ventrolateral edge of the medial lemniscus, the spinothalamic tract carries pain and temperature information from the contralateral body toward the ipsilateral thalamus and thence to somatosensory cortex.

The cranial nerve nuclei present are a different group than those present in the medulla. Only one leftover is present: a vestige of the spinal trigeminal nucleus, its rostral pole. The **facial nucleus**, the cranial nerve nucleus related to the somatomotor components of cranial nerve VII, sits ventrally in the second pie slice from the midline (see Chapter 11) as it contains motoneurons that innervate superficial facial muscles derived from branchial arches. During development, the facial motoneurons migrate dorsally toward the ventricle and then ventrally again, all the while dragging their axons behind them. This peculiar process results in a hairpin pathway for the axons of branchiomeric facial motoneurons (Fig. 12-9). The facial colliculus, the bump in the floor of the fourth ventricle (see Chapter 11), marks the **facial genu**, where these axons curve around before traveling caudally and ventrolaterally to exit from the ventral surface of the brainstem at the pontomedullary junction. Only the axons of motoneurons innervating branchial arch-derived muscles—the superficial facial muscles and the stapedius—follow the circuitous route around the abducens nucleus.

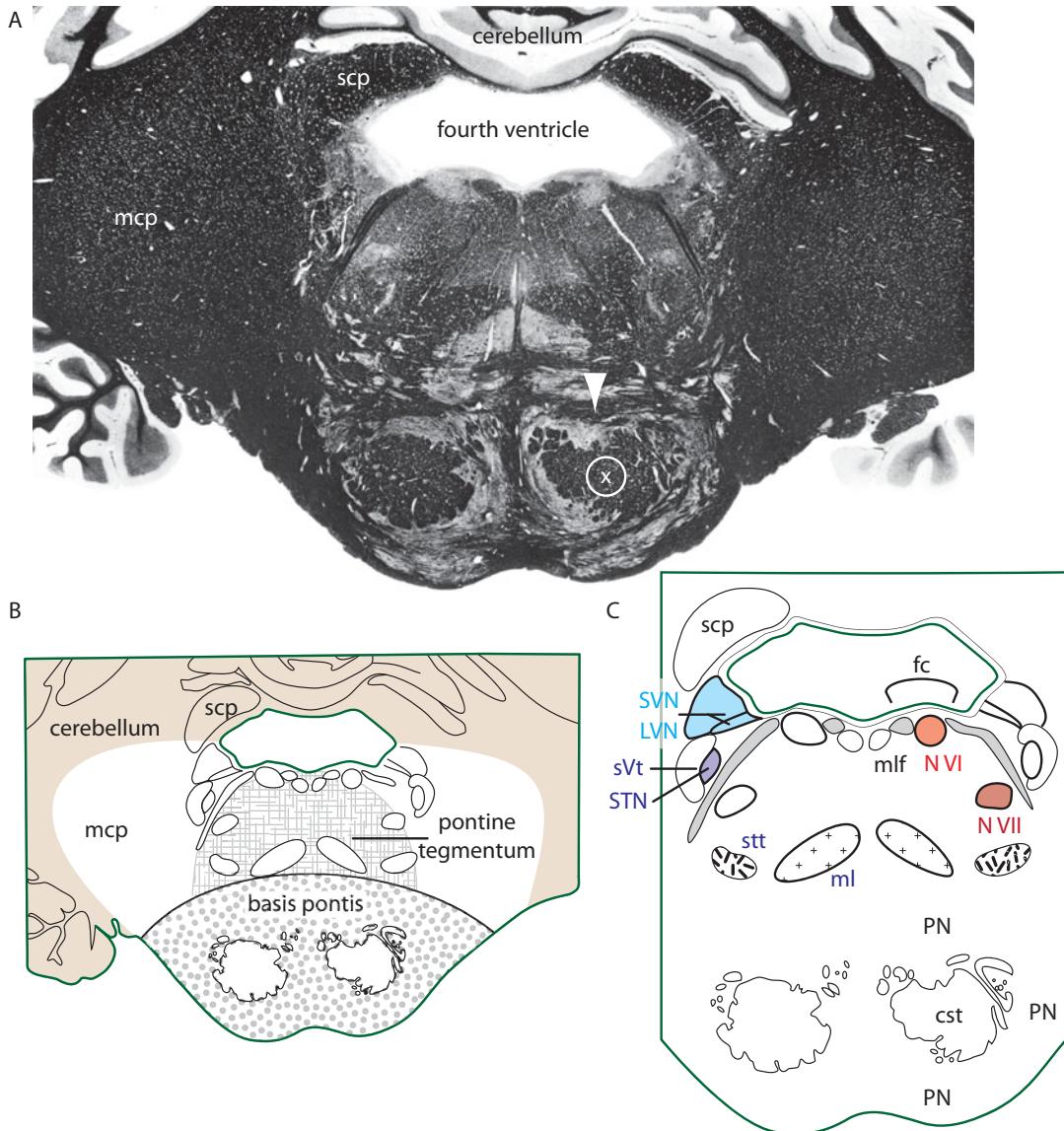
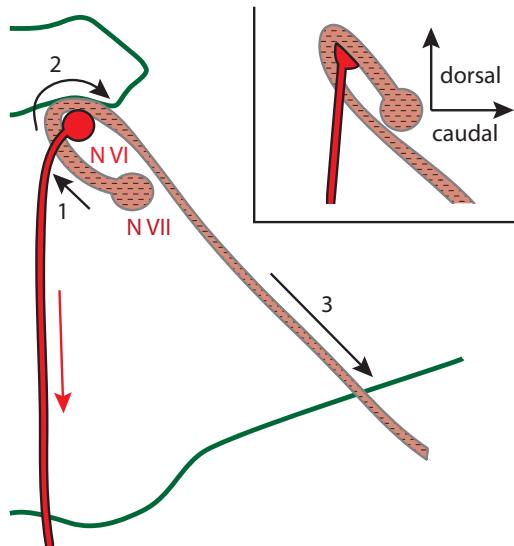


Figure 12-8. A photomicrograph (A) and diagrams (B–C) of a section through the facial colliculus are shown. The most remarkable landmarks of the pons are the basis pontis, the middle cerebellar peduncle (*mcp*), the fourth ventricle, and the overlying cerebellum. Fibers descending from the cerebral cortex include corticospinal fibers, cut in cross-section (*circled x* in A) en route to the spinal cord, and corticopontine fibers that terminate in the pontine nuclei. Pontine nuclear neurons send axons across the midline, cut longitudinally in this transverse section (arrowhead in A), and into the middle cerebellar peduncle to reach their cerebellar targets as mossy fibers. B: The pons is divided into two divisions: the ventral basis pontis and the dorsal pontine tegmentum. C: A cut out from the region illustrated in A and B is shown. The basis pontis contains bundles of corticospinal tract fibers (*cst*) amid neurons of the pontine nuclei (*PN*). The remaining structures of interest are located in the pontine tegmentum and cerebellar peduncles. The spinothalamic tract (*sTT*) travels lateral to the ventral edge of the medial lemniscus (*ml*), which is now diagonally oriented. Together, these two tracts carry all types of somatosensory information from the contralateral body. The facial nucleus (*N VII*) contains motoneurons that control the muscles of facial expression. The axons of facial motoneurons travel dorsomedially toward the fourth ventricle and then bend back around the abducens nucleus (*N VI*) to form the facial genu underlying the facial colliculus (*fc*). After the facial genu, facial motoneuron axons travel ventrolaterally and caudally from the genu to exit laterally at the level of the pontomedullary junction. The vestibular nuclei present in the mid-ppons are the superior vestibular nucleus (*SVN*) and the lateral vestibular nucleus (*LVN*). The superior cerebellar peduncle (*scp*) contains the output of the cerebellum. At its rostral pole, the spinal trigeminal nucleus (*STN*) is small in size, whereas the spinal trigeminal tract (*sVt*), containing all the inputs destined for more caudal levels, is large. The medial longitudinal fasciculi (*mlf*) remain on either side of the dorsal midline.

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Figure 12-9. Motoneuron axons that innervate facial muscles derived from branchial arches take a circuitous route within the pons. They emerge from the facial nucleus (*N VII*) located in the caudal pons to travel rostrally, medially and dorsally (arrow marked 1) to a point lateral to the midline and medial to the abducens nucleus, where they make an abrupt turn (arrow marked 2) at the facial genu. Facial axons then travel laterally around abducens and then ventrolaterally as well as caudally (arrow marked 3) to exit from the pontomedullary junction. The axons of abducens motoneurons travel directly from the abducens nucleus (*N VI*) to exit from the pontine ventricle. The inset shows a sagittal perspective of the initial facial axon trajectory, viewed from the midline. Somatosensory and visceromotor axons of the facial nerve do not take a circuitous route and emerge from the brainstem as the nervus intermedius between the main facial nerve root and the vestibulocochlear root.



Preganglionic parasympathetic neurons controlling lacrimation, nasal secretion, and salivation sit in the **superior salivatory nucleus** and send their axons directly to a ventral exit in the **nervus intermedius**, a small nerve that travels with axons from facial nucleus motoneurons and is a component of the facial nerve. Somatosensory fibers from the ear, destined for the trigeminal nuclei, and taste input destined for the nucleus of the solitary tract enter the brainstem through the nervus intermedius. Like the inferior salivatory nucleus, the superior salivatory nucleus consists of cells scattered within the reticular formation rather than an easily recognizable and distinct nuclear collection.

The **abducens nucleus** is a compact spherical nucleus containing motoneurons that innervate the lateral rectus muscle which, as you recall, abducts the eye. The abducens nucleus sits on the dorsal midline of the mid-pons, exactly the location expected for a somatomotor nucleus (see Chapter 11). The axons of abducens motoneurons travel ventrally to an exit point at the pontomedullary junction. In addition to causing abduction of the ipsilateral eye, activation of the abducens nucleus can also produce adduction of the contralateral eye through the activation of a special class of interneurons (see Chapter 26). Thus, we can think of the abducens nucleus as involved in horizontal gaze. The **paramedian pontine reticular formation**, often abbreviated as **PPRF**, abuts the abducens nucleus ventrolaterally. The paramedian pontine reticular formation contains neurons critical to controlling conjugate horizontal eye movements and this region is often termed the **horizontal gaze center** (see Chapter 26).

It is the abducens nucleus that facial axons curve around at the facial genu. Thus, it is the abducens nucleus and the facial nucleus motoneurons that form the facial colliculus. The result of this close association is the potential for impairment of both ipsilateral facial expressions and lateral eye movements by small strokes in the region.

The cochlear nucleus is restricted to the rostral medulla and absent from the mid-pons. However, within the mid-pons, two vestibular nuclei are present. The two rostral vestibular nuclei nestle within the medial aspect of the middle cerebellar peduncle,

just ventral to the superior cerebellar peduncle (Fig. 12-8). As this location suggests, the rostral vestibular nuclei are critically important in linking vestibular input with cerebellar control of eye movements, posture, and balance.

Anatomical structures that distinguish the pons are listed in Box 12-9.

THE FOURTH VENTRICLE GREATLY NARROWS IN ROSTRAL PONS

Within the rostral pons, the fourth ventricle narrows in anticipation of joining the mesencephalic cerebral aqueduct (Fig. 12-10). At this level, structures retained from more caudal levels include:

- Basis pontis containing bundles of corticospinal tract fibers and pontine nuclei
- Medial lemniscus
- Spinothalamic tract
- Medial longitudinal fasciculus
- Middle cerebellar peduncle
- Superior cerebellar peduncle.

Box 12-9

THE APPEARANCE OF THE BASIS PONTIS DISTINGUISHES PONS FROM MEDULLA.

Landmarks related to major tracts:

Pyramidal fibers, cut transversely, collect in bundles in the basis pontis.

Medial lemniscus is oriented diagonally from dorsomedial to ventrolateral.

Spinothalamic tract travels lateral to the lateral edge of the medial lemniscus.

Landmarks related to cranial nerves:

Facial nucleus: branchial motor to muscles of facial expression (VII)

Spinal trigeminal nucleus: the rostral pole is present at mid-pontine levels

Vestibular nuclei: occupy the medial and ventral portions of the middle cerebellar peduncle

Additional notable landmarks:

Pontine nuclei: information from cerebral cortex destined for the cerebellum must synapse here

Medial longitudinal fasciculus: carries axons critical to coordination of eye and head movements

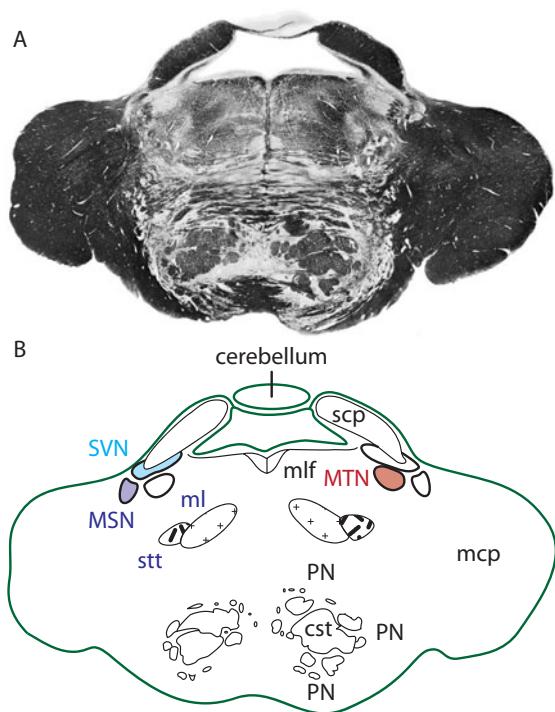
Reticular formation: fills the core with neurons and axons important to horizontal gaze and postural control

Middle cerebellar peduncle: carries cerebro-ponto-cerebellar input to the cerebellum

Superior cerebellar peduncle: carries the output of the cerebellum to the midbrain and forebrain.

Figure 12-10. A photomicrograph (A) and diagram (B) of a section through the rostral pons are shown. By now familiar landmarks include the corticospinal tract bundles (*cst*) and pontine nuclei (*PN*) of the basis pontis, the middle cerebellar peduncle (*mcp*), the fourth ventricle (not labeled), spinothalamic tract (*stt*), medial lemniscus (*ml*), and medial longitudinal fasciculus (*mlf*). The motor trigeminal nucleus (*MTN*) contains motoneurons that innervate the branchial muscles of mastication and the branchiomeric tensor tympani of the middle ear. The main sensory nucleus (*MSN*) sits lateral to the motor trigeminal nucleus and processes mainly tactile input from the face. The superior cerebellar peduncle (*scp*) has left the cerebellum en route to the midbrain and forms the lateral walls of the fourth ventricle. The rostral pole of the superior vestibular nucleus (*SVN*) is nestled below the superior cerebellar peduncle. The roof of the fourth ventricle is formed by a thin layer of non-neural tissue called the superior medullary velum (not labeled). Above the roof of the fourth ventricle, a small region of tissue from the anterior cerebellum is present in this section. Fibers descending from the cerebral cortex include corticospinal fibers en route to the spinal cord and corticopontine fibers that terminate in the pontine nuclei. Pontine nuclear neurons send axons across the midline and into the middle cerebellar peduncle (*mcp*) to reach their cerebellar targets as mossy fibers.

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Although present more caudally, the superior cerebellar peduncle is particularly well defined as it exits the cerebellum to form the eaves of the fourth ventricle rostrally (Fig. 12-10). Notice how much smaller the superior cerebellar peduncles are than the restiform bodies and middle cerebellar peduncles combined. The restiform bodies and middle cerebellar peduncles contain virtually all of the large quantity of input that enters the cerebellum, and the superior cerebellar peduncles carry most of the relatively small output. Through the peduncles, the cerebellum receives all possible data regarding movements that we want to make, as well as information on how movements are actually progressing. The cerebellum processes this information and then sends out, mostly via the superior cerebellar peduncles, either a message of “steady as she goes” or a course correction. The high input-to-output ratio of the cerebellum, about 40:1, reflects the powerful processing capacity of the cerebellum (see much more in Chapter 24).

Two nuclei related to the trigeminal nerve make their first appearances in the rostral pons. Taking the place, figuratively and literally, of the spinal trigeminal nucleus is the main or principal sensory nucleus (Fig. 12-10). Upon entering the pons, trigeminal afferents carrying low-threshold tactile and proprioceptive information turn to travel rostrally to the main sensory nucleus. Thus, roughly speaking, the main sensory nucleus is a trigeminal analog of a dorsal column nucleus as it is the first processing center for low threshold somatosensory input from the face and oral cavity. The second trigeminal-related nucleus present in the rostral pons is the motor trigeminal nucleus (Fig. 12-10), which contains branchial motoneurons that innervate the muscles of mastication and the tensor tympani, a middle ear muscle.

The landmarks of the rostral pons are listed in Box 12-10.

THE SUPERIOR CEREBELLAR PEDUNCLE AND NARROWING OF THE FOURTH VENTRICLE MARK THE ROSTRAL PONS.

Landmarks related to major tracts:

Pyramidal fibers travel in bundles in the basis pontis.

Medial lemniscus is oriented diagonally from dorsomedial to ventrolateral.

Spinothalamic tract travels lateral to the lateral edge of the medial lemniscus.

Landmarks related to cranial nerves:

Main sensory nucleus: receives somatosensory input, mainly low-threshold in nature, from the face and oral cavity

Motor trigeminal nucleus: supplies branchiomotor innervations of the muscles of mastication and the tensor tympani of the middle ear

Vestibular nucleus: the most rostral portion of the vestibular nuclei is present just ventral to the superior cerebellar peduncle

Additional notable landmarks:

Pontine nuclei: inputs from cerebral cortex destined for the cerebellum synapse here

Medial longitudinal fasciculus: carries axons critical to coordination of eye and head movements

Reticular formation: fills the core with neurons and axons important to sleep–wake control

Middle cerebellar peduncle: carries cerebro-ponto-cerebellar input to the cerebellum

Superior cerebellar peduncle: carries the output of the cerebellum to the midbrain and forebrain.

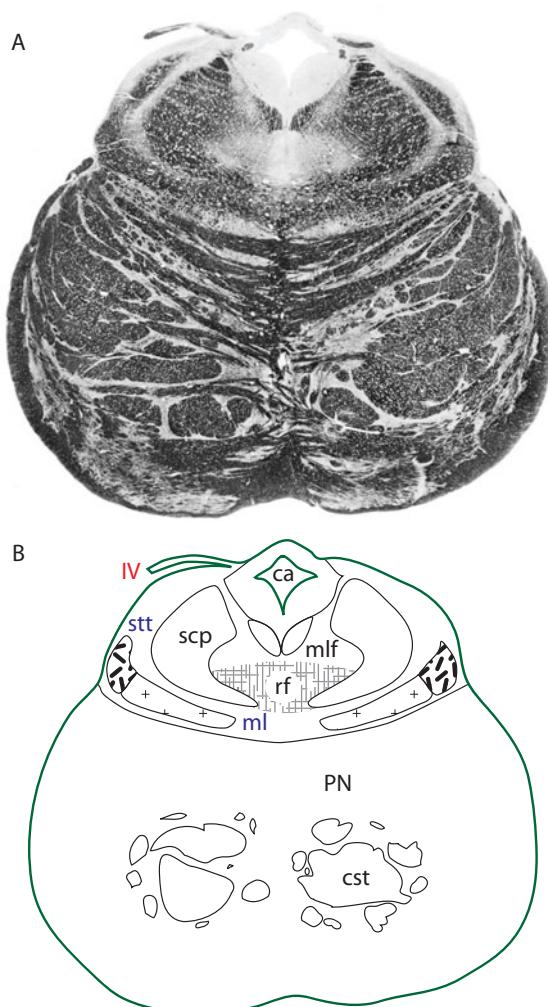
THE CEREBRAL AQUEDUCT AND EMERGENCE OF THE TROCHLEAR NERVE ROOTS MARK THE PONTOMESENCEPHALIC JUNCTION

The emergence of the trochlear nerves, from the dorsal side of the brain, marks the pontomesencephalic junction (Fig. 12-11). The trochlear nerve innervates a single extraocular muscle, the superior oblique muscle (see Chapter 10). The superior oblique, a somatic muscle, as are all the extraocular muscles, has a complex effect on the eye that depends on the starting position of the eye. When the eye starts from the neutral position, contraction of the superior oblique will cause mainly depression.

The pontomesencephalic junction features the last vestige of the basis pontis, a pontine landmark, and the first appearance of the cerebral aqueduct, the quintessential sign of the midbrain (Fig. 12-11). The narrow cerebral aqueduct is the only region of the ventricular system not to contain choroid plexus. This arrangement lessens the risk that the aqueduct will become occluded, a dangerous and potentially lethal situation (see Box 12-11).

At the pontomesencephalic junction, axons from the cerebellum traveling in the superior cerebellar peduncles turn ventrally and medially en route to crossing the midline a little more rostrally (Fig. 12-12). The medial lemniscus, carrying tactile

Figure 12-11. The exit of the trochlear nerve (IV) marks the pontomesencephalic junction shown in this photomicrograph (A) and diagram (B). The trochlear nerve, the only cranial nerve to exit from the dorsal surface of the brain, innervates the superior oblique muscle that depresses or intorts the eye, depending on initial eye position. The basis pontis containing the pontine nuclei (PN) and bundles of corticospinal tract fibers (cst) is still present. The medial lemniscus (ml), spinothalamic tract (stt), and medial longitudinal fasciculus (mlf) are in now familiar locations. At the junction of the pons and midbrain, the foremost landmark of a midbrain cross-section, the cerebral aqueduct (ca), appears. In this section, the superior cerebellar peduncles (scp) have dived deeper into the brainstem and have begun to converge toward the midline. This convergence is the start of the decussation of the superior cerebellar peduncle, or decussation of the brachium conjunctivum, which occurs just rostral to this section (see Figs. 12-12 and 12-13). Reticular formation (rf) occupies the central core region of the dorsal tegmentum. Photomicrograph reprinted and drawing modified with permission from deArmond S., et al. *Structure of the human brain: A photographic atlas*. New York: Oxford University Press, 1989.



information from the contralateral body, has shifted to an orientation that gently slopes dorsolaterally (Fig. 12-11). Immediately lateral to the medial lemniscus is the spinothalamic tract. The mesencephalic reticular formation, occupying the central portion of the section, is important in locomotion, postural control, and arousal.

The anatomical structures that mark the pontomesencephalic junction are listed in Box 12-12.

BOX 12-11

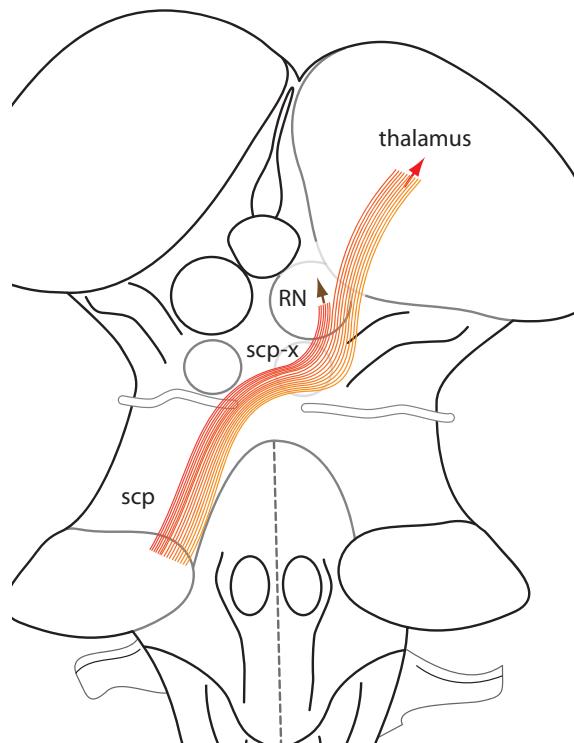
THE CEREBRAL AQUEDUCT IS VULNERABLE TO OCCLUSION.

A blockage of the cerebral aqueduct will restrict cerebrospinal fluid (CSF) flow, causing **hydrocephalus** or an elevation in intracranial pressure, a potentially lethal condition that can be treated by the surgical insertion of a shunt.

THE CAUDAL MIDBRAIN IS MARKED BY THE INFERIOR COLICULUS AND DECUSSATION OF THE SUPERIOR CEREBELLAR PEDUNCLES

The caudal midbrain is marked by the inferior colliculus and the **decussation of the superior cerebellar peduncle** also known as the **decussation of the brachium conjunctivum** (Fig. 12-13). The inferior colliculus is

Figure 12-12. Looking down on the dorsal surface of the brainstem, with the cerebellum removed, the path of the superior cerebellar peduncle (*scp*) is diagrammed. Fibers leave the cerebellum through the superior cerebellar peduncle and travel rostrally and ventrally to enter the rostral pons. These fibers cross the midline (*scp-x*) at the level of the inferior colliculus en route to midbrain and forebrain motor control centers. Axons of the superior cerebellar peduncle terminate in the red nucleus (*RN*) and the ventral anterior and ventral lateral thalamic nuclei. Because of the decussation of the superior cerebellar peduncle, the cerebellum modulates the output of the contralateral motor cortex. Consequently, the muscles on one side of the body are influenced by the contralateral motor cortex and the ipsilateral cerebellum.



important in sound localization and is a required stop for auditory information going to auditory thalamus. Just superficial to the inferior colliculus, axons from the inferior collicular nuclei form the brachium of the inferior colliculus, which carries the output of the inferior colliculus to the medial geniculate body, the auditory part of thalamus that transmits auditory information to the cortex. However, because

Box 12-12

THE TROCHLEAR NERVE EMERGES DORSALLY AT THE PONTOMESENCEPHALIC JUNCTION.

Landmarks related to major tracts:

Pyramidal fibers travel in bundles in the basis pontis.

Medial lemniscus has shifted to a gentle arc from ventromedial to dorsolateral.

Spinothalamic tract continues to travel lateral to the lateral edge of the medial lemniscus.

Landmarks related to cranial nerves:

Trochlear roots: somatic motoneurons that innervate the superior oblique muscle via cranial nerve IV

Additional notable landmarks:

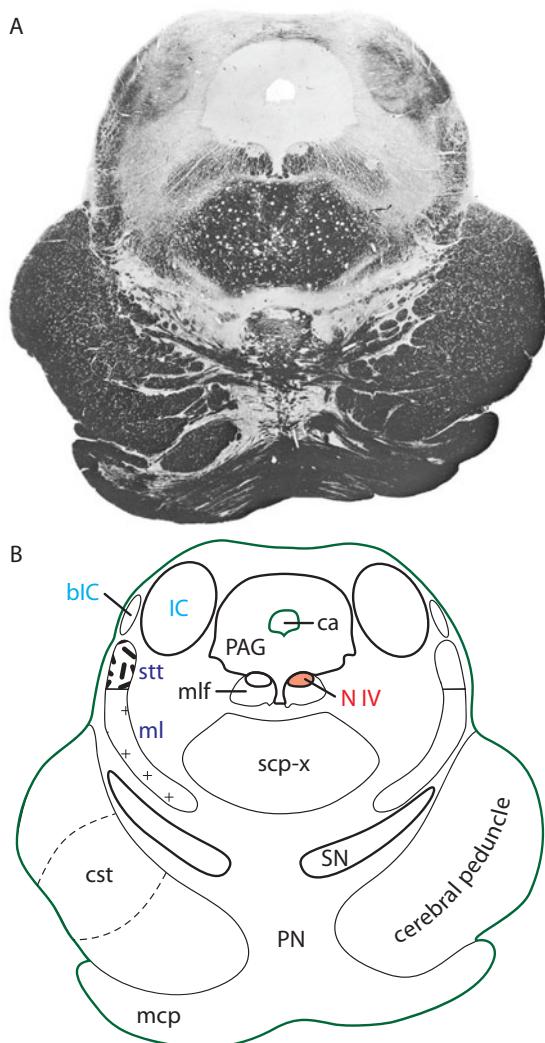
Pontine nuclei: neurons receive input from cerebral cortex and project into the cerebellum

Medial longitudinal fasciculus: carries axons critical to coordination of eye and head movements

Superior cerebellar peduncle: carries the output of the cerebellum to the midbrain and forebrain.

Figure 12-13. A photomicrograph (A) and diagram (B) of a section through the caudal midbrain are shown. The basis pontis is largely gone, although small regions of pontine nuclei (PN) and mossy fibers destined for the middle cerebellar peduncle (mcp) remain. Taking the place of the basis pontis are the cerebral peduncles that mark the midbrain ventrum. The corticospinal tract (cst) travels in the middle third of the cerebral peduncle. The medial lemniscus (ml) and spinothalamic tract (stt) are in familiar locations. The cerebral aqueduct (ca) is present throughout the midbrain. Surrounding the aqueduct is the periaqueductal gray (PAG), a region that is important in coordinating homeostatic behaviors. The trochlear nucleus (N IV) is a small nucleus nestled within the medial longitudinal fasciculus (mlf) that, along with the inferior colliculus (IC) and decussation of the superior cerebellar peduncle (scp-x) distinguish the caudal midbrain. The output of the inferior colliculus carries bilateral auditory information through the brachium of the inferior colliculus (bIC) to the medial geniculate nucleus of the thalamus. Dorsal to the cerebral peduncle is the caudal pole of the substantia nigra (SN), an important component of basal ganglia circuits.

Photomicrograph reprinted and drawing modified with permission from deArmond S., et al. *Structure of the human brain: A photographic atlas*. New York: Oxford University Press, 1989.



auditory pathways are bilateral beyond the cochlear nucleus and thus not impaired by localized lesions, we do not further detail central auditory pathways.

Fibers in the superior cerebellar peduncle cross the midline through the decussation of the superior cerebellar peduncle (Figs. 12-12 and 12-13). Because of this decussation, cerebellar information about ipsilateral movements is carried across the midline to contralateral motor control centers in the forebrain. In this way, movements on one side of the body are controlled by the contralateral motor cortex and smoothed by the ipsilateral cerebellum (see Fig. 11-3).

Surrounding the aqueduct is an easily recognized donut-shaped area of gray matter termed the **periaqueductal gray**. The periaqueductal gray can be considered a caudal extension of the hypothalamus (see Chapter 13) and plays a critical role in coordinating homeostasis with motor behavior during mating, fighting, recuperation from injury, and so on.

Another landmark of the caudal midbrain is the **trochlear nucleus**, which nestles within the medial longitudinal fasciculus like an apple cupped in a hand (Fig. 12-13). The trochlear nucleus is small as it contains motoneurons innervating a single muscle, the superior oblique. The axons of trochlear motoneurons travel

caudally and dorsally to exit (Fig. 12-11). Upon exiting, the axons cross, so that the right trochlear nucleus innervates the left superior oblique and vice versa.

Corticospinal tract fibers from the basis pontis feed into the middle third of the cerebral peduncles which mark the midbrain ventrum. Axons within the cerebral peduncles on either side of the corticospinal fibers are corticopontine fibers from either frontal or posterior regions of cerebral cortex. Corticobulbar fibers, headed for the motor trigeminal, facial, and hypoglossal nuclei travel with the corticospinal fibers in the middle third of the cerebral peduncle. The locations of the medial lemniscus and spinothalamic tract are slowly shifting dorsally as we move from pons, rostrally through midbrain. In the caudal midbrain, the spinothalamic tract is just ventral to the inferior colliculus, and the medial lemniscus is ventromedial to the spinothalamic tract.

Dorsal to each cerebral peduncle stretches an arc of gray matter called the *substantia nigra*. The substantia nigra has two parts or *pars*, which have nothing in common beyond their neighboring locations. The *pars reticulata* is an output nucleus of the basal ganglia and resembles the internal portion of the *globus pallidus* (see Chapter 13). In fact, the internal globus pallidus and pars reticulata are separated by the internal capsule and cerebral peduncles during development (see Chapter 3). As detailed in Chapter 25, substantia nigra pars reticulata sends out a continuous “don’t move” signal, which is only interrupted when a movement occurs. In the case of the major projection from pars reticulata to the superior colliculus, the continuous inhibitory signal prevents eye movements. When the inhibitory signal is briefly interrupted, the superior colliculus’ plan for an orienting movement is released from suppression and thus is enacted.

The substantia nigra *pars compacta* consists of a group of dopaminergic cells that project heavily into the striatum of the basal ganglia. The roles of these dopaminergic cells are many, varied, and controversial. One clear role for nigral dopaminergic cells is to provide the “oil” necessary for movement. When pars compacta cells die, as occurs in *Parkinson’s disease*, people do not initiate movements or do so very slowly and infrequently (see much more in Chapter 25).

The structures that mark the caudal midbrain are listed in Box 12-13.

ROSTRAL MIDBRAIN IS MARKED BY THE OCULOMOTOR NUCLEUS, SUPERIOR COLICULUS, AND RED NUCLEUS

Within the rostral midbrain, the cerebral peduncles, containing the corticospinal and corticobulbar tracts, are well developed (Fig. 12-14). Exiting from the medial edge of the cerebral peduncles are the roots of the oculomotor nerve. The *oculomotor nucleus*, a large sprawling nucleus, occupies the midline just ventral to the aqueduct. Recall that the oculomotor nucleus contains somatic motoneurons that innervate five different muscles:

- Medial rectus, an extraocular muscle that adducts eye
- Inferior rectus, an extraocular muscle that depresses the eye

THE CAUDAL MIDBRAIN IS DISTINGUISHED BY THE INFERIOR COLICULI AND THE DECUSSTATION OF THE BRACHIUM CONJUNCTIVUM.

Landmarks related to major tracts:

Pyramidal fibers travel in the middle third of the cerebral peduncle contralateral to the muscles that they ultimately control.

Medial lemniscus fibers continue to shift laterally.

Spinothalamic tract travels dorsal to the medial lemniscus.

Landmarks related to cranial nerves:

Trochlear nucleus: somatic motoneurons that innervate the superior oblique muscle via the trochlear nerve

Additional notable landmarks:

Cerebral peduncle: carries the corticospinal and corticobulbar tracts in the middle third and corticopontine fibers on either side

Medial longitudinal fasciculus: carries axons critical to coordination of eye and head movements

Decussation of the superior cerebellar peduncle: carries cerebellar output to the contralateral midbrain and thalamus

The caudal pole of the substantia nigra, a critical region for the timing and initiation of movements, caps the cerebral peduncles.

- Superior rectus, an extraocular muscle that elevates the eye
- Inferior oblique, an extraocular muscle that elevates the eye
- Levator palpebrae, a muscle involved in elevating the *eyelid* voluntarily.

Also contributing to the oculomotor nerve is the **Edinger-Westphal nucleus**, which sits cradled within the oculomotor nucleus (Fig. 12-14C). The Edinger-Westphal nucleus contains visceromotor neurons that control pupillary constriction and lens shape via projections to the parasympathetic ciliary ganglion (see Chapter 10). Together, the oculomotor and Edinger-Westphal nuclei comprise the **oculomotor complex**. The medial longitudinal fasciculus is a highway dedicated to coordinating head and eye movements, and is situated just lateral to the oculomotor complex.

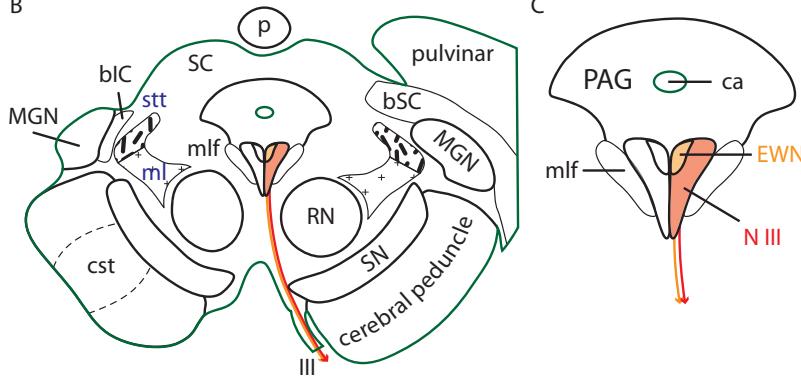
Motoneurons in the oculomotor nucleus innervate three of the four extraocular muscles involved in vertical eye movements. The remaining extraocular muscle involved in moving the eye vertically is innervated by motoneurons in the trochlear nucleus located just caudal to the oculomotor complex. Neurons that *coordinate* vertical gaze comprise the **vertical gaze center**, which is located adjacent to the medial longitudinal fasciculus at the level of the oculomotor complex.

The medial lemniscus and spinothalamic tract retain the same positions they occupied more caudally, although the surrounding landscape has changed. Instead of sitting near the edge of the brain, these somatosensory tracts now are positioned deep to the medial geniculate body and its afferent input, the brachium of the inferior colliculus. Because hearing from each ear is bilaterally represented in the brain above the medulla, even a lesion of the medial geniculate body does not noticeably alter hearing.

A



B



C

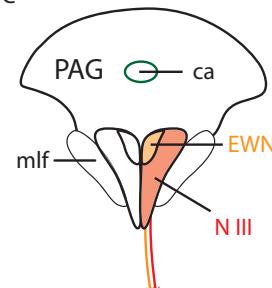


Figure 12-14. A photomicrograph (A) and diagrams (B–C) of a section through the superior colliculus (SC) are shown. B: At this level, the corticospinal tract (cst) travels in the middle third of the cerebral peduncle en route to the contralateral ventral horn. The medial lemniscus (ml) and spinothalamic tract (stt) continue to travel dorsal to the lateral edge of the cerebral peduncles. The red nucleus (RN), a motor control center, is evident as a large spherical nucleus. The substantia nigra (SN) is a clearly delineated gray matter region (unstained by myelin stains), which caps the cerebral peduncles. C: A magnified view of the central gray is illustrated. The oculomotor complex consists of the oculomotor nucleus (N III) and the Edinger-Westphal nucleus (EWN). Recall that the oculomotor nucleus contains somatic motoneurons that innervate four extraocular muscles and the levator palpebrae, a muscle that raises the eyelid. The Edinger-Westphal nucleus contains autonomic motor neurons that innervate parasympathetic neurons in the ciliary ganglion, ultimately influencing pupillary diameter and lens shape. Axons from both oculomotor and Edinger-Westphal nuclei course ventrally and exit the midbrain just medial to the cerebral peduncles (III in A and B). The medial longitudinal fasciculus (mlf) is located just lateral to the oculomotor complex (B–C). The periaqueductal gray (PAG) continues to surround the cerebral aqueduct (ca) in the rostral midbrain. Although this section contains several structures of the rostral midbrain, it also contains a number of diencephalic structures including the medial geniculate nucleus (MGN), a thalamic nucleus that processes auditory information, and the pulvinar, a caudal thalamic nucleus involved in visual processing. The brachium of the inferior colliculus (bIC) carrying input to the medial geniculate nucleus is located just medial to the nucleus. The brachium of the superior colliculus (bSC) carries visual information from the superior colliculus to the lateral geniculate nucleus (not present at this level) and to the pulvinar. Finally, nestled between the superior colliculi is the pineal gland (P), a non-neuronal gland that secretes melatonin.

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Just as the inferior colliculi are landmarks of the caudal midbrain, the superior colliculi are a sure indication of the rostral midbrain. The superior colliculus is important in transforming multimodal sensory information, input from multiple senses, into a motor command for orienting movements. Thus, the superior colliculus is critical to shifting gaze toward unexpected stimuli. In lower animals without a well-developed cerebral cortex, the superior colliculus coordinates most visually

driven behavior. In humans and other primates, the superior colliculi retain the capacity to drive orienting movements toward moving stimuli. This ability underlies blindsight, a condition in which patients orient toward moving objects but do not “see” them (see Chapter 16). In blindsight, the inability to perceive and describe objects results from damage to visual cortex, while the intact and undamaged superior colliculus supports the ability to react to moving stimuli.

The substantia nigra is more fully developed in the rostral midbrain than in the caudal midbrain. In the rostral midbrain, the substantia nigra caps most of the width of the cerebral peduncles. Dorsal to the substantia nigra are large spherical nuclei that straddle the midline. These nuclei are the **red nuclei** and form clear landmarks of the rostral midbrain. The red nuclei receive input from the cerebellum and from motor cortex, and are the source of the **rubrospinal tract**, an important descending motor pathway. Hanging over the midbrain is a large thalamic nucleus called the **pulvinar**.

The landmarks of the rostral midbrain are reviewed in Box 12-14.

THE POSTERIOR COMMISSURE MARKS THE MESODIENCEPHALIC JUNCTION

As the midbrain meets the diencephalon, the cerebral aqueduct elongates ventrally to form a slit; this is the opening of the third ventricle (Fig. 12-15). At this point, a transverse slice contains even more of a mixture of the two

Box 12-14

THE SUPERIOR COLICULUS IS THE MAJOR EXTERNAL MARKER OF THE ROSTRAL MIDBRAIN.

Landmarks related to major tracts:

Pyramidal fibers travel in the middle third of the cerebral peduncle contralateral to the muscles that they ultimately control.

Medial lemniscus fibers continue to shift laterally.

Spinothalamic tract travels just deep to the medial geniculate nucleus and the brachium of the inferior colliculus.

Landmarks related to cranial nerves:

Oculomotor nucleus: somatic motoneurons that innervate four extraocular muscles and the levator palpebrae

Edinger-Westphal nucleus: visceromotor neurons that control pupillary constriction and lens accommodation via parasympathetic projections to the ciliary ganglion

Additional notable mesencephalic landmarks:

Cerebral peduncle: carries the corticospinal and corticobulbar tracts in the middle third and corticopontine fibers on either side

Medial longitudinal fasciculus: carries axons critical to coordination of eye and head movements

Substantia nigra: an important component of the basal ganglia and consists of two very different parts

Superior colliculus: critical to visually guided movements and orienting movements to moving objects

Pineal gland: non-neural tissue that secretes melatonin and is important in the coordination of circadian rhythms.

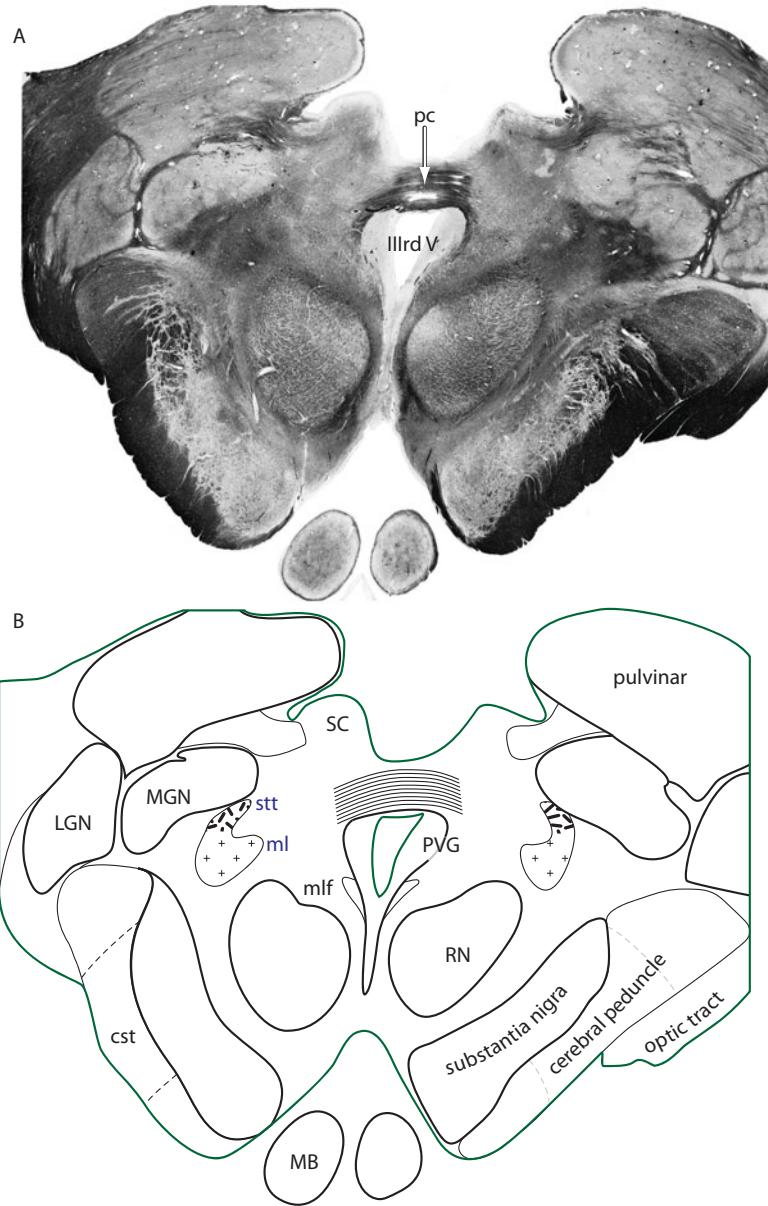


Figure 12-15. A photomicrograph (A) and diagram (B) of a section through the mesodiencephalic junction are shown. In large part, midbrain features are concentrated centrally and diencephalic structures populate the edges. The cerebral aqueduct has elongated dorsoventrally as it transforms into the third ventricle (*IIIrd V* in A). The corticospinal tract (*cst*) continues to travel in the middle third of the cerebral peduncles. Although still present, the cerebral peduncles are oriented more dorsoventrally than is the case more caudally. Just anterior to this section, axons from the cerebral peduncles join the internal capsule of the forebrain. As they near their thalamic destination, the medial lemniscus (*ml*) and spinothalamic tract (*stt*) are poorly delineated. Consequently, damage in this region usually impairs the function of both pathways. Midbrain landmarks in this section include the red nucleus (*RN*), substantia nigra, and superior colliculus (*SC*). The rostral pole of the medial longitudinal fasciculus (*mlf*) is located just lateral to the periventricular gray (*PVG*), which surrounds the caudal third ventricle. Although there are no extraocular motoneurons present at this level, there are nuclei important in gaze control within the periventricular gray. Therefore, the medial longitudinal fasciculus at this level serves to connect gaze control centers with more caudal areas containing extraocular and neck motoneurons. Capping the aqueduct is the posterior commissure (*pc* in A and lines in B), an easily visualized and therefore useful landmark in magnetic resonance images (MRIs). Diencephalic structures present include the medial geniculate nucleus (*MGN*) and its lateral neighbor, the lateral geniculate nucleus (*LGN*), a critical thalamic nucleus for vision (see Fig. 10-3). The pulvinar, another thalamic nucleus important in vision, appears as a pillow (*pulvinar* is Latin for cushion or pillow) atop the section. The optic tract (*ot*) carries visual information from the retina into the lateral geniculate nucleus, wrapping around the cerebral peduncles along the way. The superior colliculus also sends fibers, albeit fewer than does the retina, through the brachium of the superior colliculus (*bIC*) into the lateral geniculate nucleus and the pulvinar. The neighboring positions of the optic and corticospinal tracts underlie the fairly common combination of contralateral paralysis and hemianopia due to damage in this region. Finally, the mammillary bodies (*MB*), important in memory formation, float below the midbrain, as they attach to the ventrum of the diencephalon more rostrally.

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Box 12-15

A LINE BETWEEN THE POSTERIOR AND ANTERIOR COMMISSURES ORIENTS MAGNETIC RESONANCE IMAGES (MRIs).

The posterior commissure in the midbrain and the anterior commissure in the forebrain are easily visualized landmarks in MRIs. Therefore, the line between the two commissures, termed the **ACPC line**, sets up the **Talairach coordinate frame** for brain MRIs. Talairach coordinates are now in standard use for mapping the location of brain structures and lesions.

bordering regions than occurs at either the spinomedullary or pontomesencephalic junctions. This is simply because the brain does not develop in register with a grid, so that the actual demarcation between midbrain and diencephalon is not a flat plane.

Clear signs of the midbrain at the mesodiencephalic junction include:

- *Red nucleus*: the source of the rubrospinal tract important in descending motor control
- *Superior colliculus*: a region important in coordinating orienting movements
- *Cerebral peduncles*: containing corticospinal, corticobulbar and corticopontine fibers
- *Substantia nigra*: consisting of the pars reticulata, carrying the output of the basal ganglia to targets including the superior colliculus, and the pars compacta, the source of dopamine in the striatum
- *Posterior commissure*: connects fibers on either side of the dorsal midbrain important in coordinating a bilateral reaction to visual stimuli (see Box 12-15)

The medial lemniscus and spinothalamic tracts remain in about the same relative location as more caudally as they near their targets in the posterior thalamus. Three thalamic nuclei are already visible:

- The medial geniculate nucleus processes auditory information from both ears and projects to the primary auditory cortex.
- The lateral geniculate nucleus processes visual information from the contralateral half of the visual field and projects to the primary visual cortex, also known as **striate cortex**.
- The pulvinar receives multimodal sensory inputs but serves as a primarily visual processing region in the posterior thalamus.

Although not attached to the brain at this point, the **mammillary bodies**, an important part of the “limbic system” involved in memory, are seen floating below the section. The mammillary bodies receive inputs from the hippocampus, via the fornix, and from the amygdala (see Chapter 13). The mammillary bodies in turn project to the **anterior nucleus** of the thalamus via the **mammillothalamic tract**. This circuitry, discussed in greater depth in Chapter 13, is part of the **Papez circuit**, which is important in both memory and emotion (see Box 12-16).

The mixture of mesencephalic and diencephalic structures present at the midbrain-diencephalon junction are listed in Box 12-17.

Box 12-16

THE MAMMILLARY BODIES ARE CRITICAL TO THE FORMATION OF MEMORIES.

The mammillary bodies degenerate as a result of thiamine deficiency, giving rise to an amnesic syndrome called **Korsakoff syndrome**. Korsakoff syndrome, common in patients with advanced alcoholism, causes a deficit in explicit memory while leaving implicit memory relatively intact. An illustrative story involves the neurologist Éduard Claparède, who placed a pin in his hand and then

shook hands with a Korsakoff syndrome patient, causing the patient to experience a brief pricking pain. On the following day, despite having no recall of ever meeting Dr. Claparède, the patient refused to shake the physician's hand. Such subconscious memories that influence our actions without producing conscious awareness are termed *implicit memories*.

Box 12-17

THE APPEARANCES OF DIENCEPHALIC NUCLEI, THE POSTERIOR COMMISSURE AND THE THIRD VENTRICLE MARK THE MESO-DIENCEPHALIC JUNCTION.

Landmarks related to major tracts:

Pyramidal fibers travel in the middle third of the cerebral peduncle, which is about to merge with the internal capsule of the forebrain.

Medial lemniscus fibers continue in the same relative position as they were more caudally.

Spinothalamic tract fibers continue in the same relative position as they were more caudally.

Landmarks related to cranial nerves:

None present at this level

Additional notable landmarks:

Cerebral peduncle: shifts its orientation to transition into the internal capsule of the forebrain

Substantia nigra: an important component of the basal ganglia consisting of two very different parts

Superior colliculus: critical to visually guided movements and orienting movements to moving objects

Posterior commissure: joins the two sides of the tectum and provides a clear landmark for imaging studies

Optic tract: refers to retinal fibers between the optic chiasm and the lateral geniculate nucleus

Medial geniculate nucleus: receives auditory input from the inferior colliculus and projects to auditory cortex

Lateral geniculate nucleus: receives retinal input and projects to visual cortex

Pulvinar: a caudal thalamic nucleus important in processing visual inputs.

THE BRAINSTEM IS THE JACK-OF-ALL-TRADES OF THE NERVOUS SYSTEM

As diencephalic structures begin to overrun midbrain cross-sections, it is time to look back at our journey and to appreciate the “heavy-lifting” accomplished by the brainstem. The jack-of-all-trades character of the brainstem matches the array of functions served by specialized tissues of the head. The head has a mouth, ears, eyes, and an airway that supports breathing and speech. The brainstem *serves* the head, enabling the varied tissues of the head to look around, hear, speak, ingest solids and liquids, maintain a desired posture, and sense position with respect to gravity. The brainstem even contributes to the control of visceral function. The functions of the spinal cord are less varied, being restricted to somatosensory, somatomotor, and autonomic motor functions. The concrete functions of the forebrain—smell, vision, hormone release—are also fewer than those of the brainstem. Because the brainstem is so integral to life as we know it, even a small lesion within the brainstem can be devastating, almost inevitably damaging multiple functions.

Hopefully, placing the brainstem in a larger perspective will help you realize the importance and worth of the material that you have taken the effort to learn in this chapter. Understanding and remembering the functions and structure of the brainstem takes effort and can feel overwhelming. Yet, millimeter for millimeter or milligram for milligram, the brainstem is worth it in terms of diagnostic power. Indeed, from the perspective of the brainstem, the forebrain is *easy*. So, onward to the easy part of the brain!



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CHAPTER 13

FOREBRAIN: ACTION, PERCEPTION, EMOTION, THOUGHT

The deeply complex forebrain provides the substrate that infuses movements, stimuli, and situations with meaning. As hard it is to identify any single forebrain feature that distinguishes us from other animals, it is clear that the collective properties of the forebrain are responsible for making us “human.” The forebrain transforms movement into action, sensation into perception, and allows for the rich experiences of emotion and thought. Without the forebrain, we may be able to function physiologically, at least in forgiving conditions, but we could not do the things we do. We could not build libraries, cook delicious meals, or create music. The forebrain leaves the hard work of keeping us alive to the brainstem and spinal cord while taking full credit and holding complete responsibility for all the lofty functions that we enjoy. In essence, “life” is possible, but certainly not as rich without the myriad contributions of the forebrain (see Box 11-1).

FOREBRAIN STRUCTURES CAN BE LUMPED INTO SEVERAL FUNCTIONAL GROUPINGS

The student who is new to the human brain and trying to learn forebrain anatomy faces an enormous challenge. First, the human telencephalon has taken certain twists and turns that render visualizing it in three dimensions tricky and confusing. Second, the functions of the telencephalon are more complex and nuanced than those of the cranial nerves, spinal cord, and long pathways. In this chapter, text is used to describe forebrain functions, while illustrations and captions are used to communicate the anatomy of forebrain structures.

To start with, we divide up the forebrain into its most important components (Fig. 13-1):

- Diencephalon
 - The hypothalamus is critical to maintaining body homeostasis, responding to physiological challenges, and to expressing emotions. The hypothalamus also exerts control over the pituitary gland.

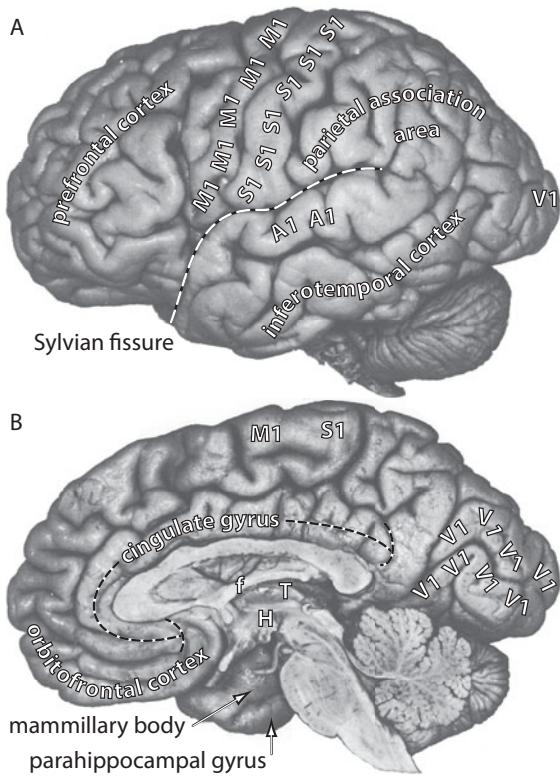


Figure 13-1. In a lateral view of the brain (A), the only part of the forebrain visible is the cerebral cortex. Primary motor (**M1**), somatosensory (**S1**), and auditory (**A1**) cortices, and a small bit of primary visual cortex (**V1**) are evident. The large Sylvian fissure or lateral sulcus (dashed line) divides the temporal cortex, housing auditory cortex, from parietal and frontal cortices, whereas the central sulcus (not labeled) separates the M₁-containing frontal lobe from the S₁-containing parietal lobe. Additional cortical areas visible are the prefrontal cortex, an area critical to organizing behavior, parietal association cortex where sensory inputs are integrated, and inferotemporal cortex where visual objects are identified and their meaning understood. Insular cortex, sometimes considered the fifth lobe, is deep within the Sylvian fissure and not visible from either the lateral or medial surfaces of the cerebral cortex (see Fig. 13-3). When the brain is cut in half sagittally and viewed from the medial surface (B), the relatively small thalamus (**T**) is evident. Ventral to the thalamus is the hypothalamus (**H**). This mid-sagittal view of the brain reveals most of primary visual cortex and small bits of primary motor and somatosensory cortices. The cingulate gyrus, posterior part of the orbitofrontal cortex, parahippocampal gyrus, and fornix (**f**) wrap around the diencephalon. Along with the hypothalamus, mammillary bodies, and amygdala (not shown), these structures constitute the limbic system (Fig. 13-2).

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- The thalamus forms the bulk of the adult diencephalon and includes about a dozen nuclei with functions primarily focused on sensory, motor, emotional or executive processing.
- Telencephalon
 - The cerebral cortex (see Box 13-1) occupies the outer rind, or mantle, of the telencephalon and includes numerous areas that contribute to a large number of functions. In this chapter, we introduce the following general areas:
 - Primary sensory cortices are essential way-stations for somatosensory, visual, auditory, and gustatory perception. The primary motor cortex is essential for volitional or voluntary movements.
 - Frontal cortex contains a number of motor-related areas, as well as the **prefrontal cortex** involved in executive function.

CORTEX IS A LAMINATED STRUCTURE ON THE OUTER SURFACE OF A NERVOUS STRUCTURE.

Cortex is defined by three features:

- Cortex is located superficially in a nervous structure.
- Cortex is laminated or layered.
- Cortex contains a prominent neuronal type with a dendrite that stretches toward a cell-poor layer, termed the **molecular layer**, at the pial surface. This dendrite is called the **apical dendrite**.

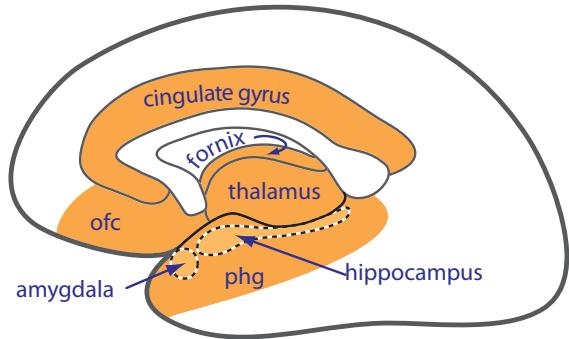
The mammalian brain has two regions of cortex, one in the cerebellum and one in the cerebrum. In cerebellar cortex, there are three laminae; it is the

cerebellar **Purkinje cell** that has an apical dendrite that extends superficially.

Cerebral cortex contains the prominent pyramidal cell that extends an apical dendrite into the most superficial molecular layer. Cerebral cortex is heterogeneous with from three to six layers, and with each layer varying in thickness across the cortical sheet. The cerebral cortex marked by six layers is termed **neocortex**, and it is this type of cortex that is greatly expanded in the primate, including humans. It should be noted that more often than not, when the term *cortical* is used alone without a qualifier, it refers to *cerebral* cortex and not cerebellar cortex.

- Parietal cortex is critical to associating visual, somatosensory, and other sensory information for use in both perception and motor control.
- Circuits in **inferotemporal cortex** support recognition of the sensory world and translate sensory representations into meaning.
- The hippocampus, part of the temporal cortex, encodes new **declarative**, or factual, memories. Information arrives in the hippocampus, and memories are shipped out of the hippocampus to other regions of cerebral cortex for storage. The route out of the hippocampus passes through the **parahippocampal gyrus**.
- **Limbic** structures do not participate in either sensory or motor processing but rather contribute to emotional processing and to learning and memory. Today, most consider the hippocampus, parahippocampal gyrus, **cingulate gyrus**, and **orbitofrontal cortex** (Fig. 13-2) along with a number of subcortical and brainstem regions as limbic (see Box 13-2).
 - Telencephalic structures deep to the outer rind of cortex are termed **subcortical** (Fig. 13-3). There are two primary subcortical cell groupings:
 - The basal ganglia are a conceptual grouping of nuclei centered upon the caudate, putamen, and globus pallidus, all three of which develop from the telencephalic ganglionic eminences.
 - The amygdala (Fig. 13-3C) is critical to processing emotional input and forming emotional memories.

Figure 13-2. Paul Broca, a French neurologist who made numerous and varied contributions to our understanding of forebrain function, originally used the term, “limbic” to refer to structures that border (limbus is the Latin word for border) the diencephalon. These structures included the cingulate gyrus, hippocampus, orbitofrontal cortex (oFC), parahippocampal gyrus (PHG), and fornix. Today, anterior thalamus, amygdala, and the hypothalamus including the mammillary bodies, are also considered to be limbic structures.



- And several subcortical white matter tracts:
 - The **corona radiata** makes up the bulk of the white matter immediately underlying the cerebral cortex and thus provides the main access route to and from cortex (Fig. 13-4A).
 - The internal capsule is deep to the corona radiata (Fig. 13-4B) and contains axons that descend from the telencephalon to the midbrain, hindbrain, and spinal cord. This includes axons of the corticospinal and corticobulbar tracts. Axons from the telencephalon to the

Box 13-2

LIMBIC IS A TERM THAT REFERS TO PARTS OF THE BRAIN INVOLVED IN EMOTIONAL PROCESSING AND LEARNING AND MEMORY.

The term *limbic* derives from the Latin word for border, and as originally defined by Paul Broca, refers to telencephalic structures that border the diencephalon (Fig. 13-2). Today, the term is used to refer to structures that are central to emotional processing, learning, and memory but do not participate directly in either sensory or motor processing.

Limbic structures communicate at least in part through the Papez circuit (Fig. 13-2). The circuit as originally proposed by James Papez, an early 20th-century neurologist, links the hippocampus to the mammillary bodies by way of the fornix, the mammillary bodies to the anterior nucleus of the thalamus, the anterior nucleus to the cingulate gyrus, and the cingulate gyrus to the parahippocampal gyrus, and then to the hippocampus. This proposed circuit is important as it provides a pathway by which very important and widely separated parts of the brain can talk to each other. Yet, additional regions

critical to emotions and/or learning and memory include structures that are not part of the Papez circuit as originally described:

- Mediodorsal nucleus of the thalamus
- Amygdala
- Hypothalamic nuclei including but not restricted to the mammillary bodies
- Orbitofrontal cortex

Even this extended list of limbic structures is not complete as several brainstem structures are also required for emotional processing. Finally, many connections, in addition to those of the Papez circuit, certainly contribute to limbic function. A thorough understanding of the connections and circuits underlying emotional processing presents an important challenge for the future.

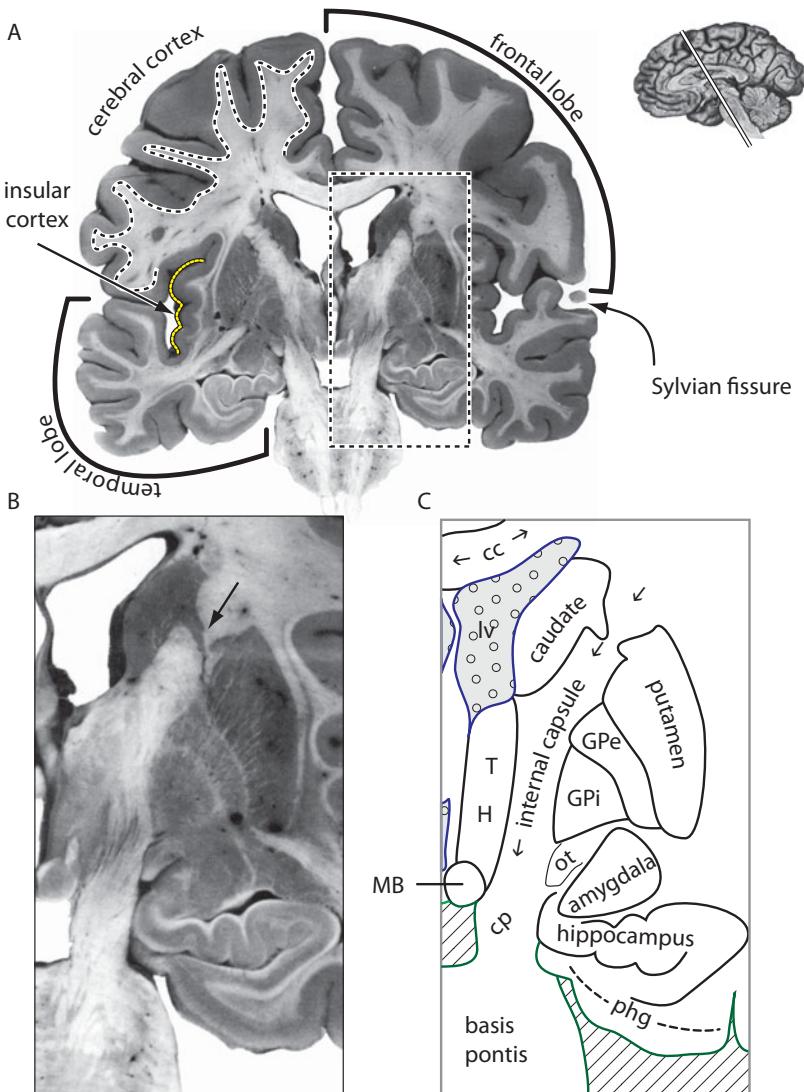


Figure 13-3. An unstained cross-section through the temporal and frontal lobes, at the level and angle shown in the inset, is shown. Since this section is unstained, regions containing neurons are gray in color and regions with myelinated axons are white in color. The region in the dashed box in A is shown at greater magnification in B and C. **A:** The gray matter mantle of the telencephalon is the cerebral cortex. The insular cortex is located deep within the Sylvian fissure. **B-C:** The hippocampus is a region of **archicortex**, or old cortex, that has only three laminae rather than the six layers that defines neocortex. Structures deep to the cortex (dashed line at top left of A) are termed **subcortical**. The major subcortical components of the telencephalon are the core components of the basal ganglia, namely the caudate, putamen, external or lateral globus pallidus (**GPe**), and internal or medial globus pallidus (**GPI**). The caudate and putamen are split apart by fibers of the internal capsule during development. Nonetheless, occasional cellular bridges across the internal capsule between the caudate and putamen (arrow in B) remain in the adult brain. The striatum, consisting of the caudate and putamen, as well as the pallidum, the external and internal globus pallidus, develop from the ganglionic eminences (see Chapter 3). The amygdala is the other major subcortical telencephalic structure beyond the striatum and pallidum. Additional structures labeled for orientation are the corpus callosum (**cc**), lateral ventricle (**lv**), thalamus (**T**), hypothalamus (**H**), the optic tract (**ot**), mammillary bodies (**MB**), cerebral peduncles (**cp**), basis pontis, and parahippocampal gyrus (**phg**). Ventricular areas are filled with a pattern of circles on a pale blue background. Areas that are outside of the brain are filled with diagonal lines.

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diencephalon and from the diencephalon to the telencephalon also travel in the internal capsule. Among the axons ascending to cortex from thalamus are the thalamocortical axons in the two long somatosensory pathways, the dorsal column-medial lemniscus and spinothalamic pathways.

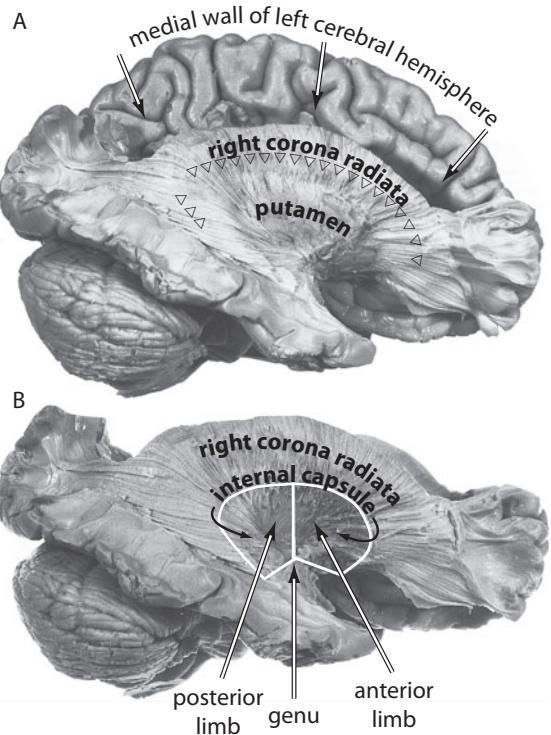


Figure 13-4. The corona radiata and internal capsule have been revealed by dissecting away the right cerebral cortex, leaving the right corona radiata evident and, as shown in A, exposing the medial wall of the left hemisphere. The corona radiata carries all axons that travel between the cerebral cortex and subcortical structures. The arrowheads in A point to the place where the corona radiata turns into the internal capsule. In the dissection in A, the putamen has been left in place and therefore obscures most of the internal capsule from view. In B, the putamen is dissected away, and the left hemisphere removed all together, exposing the internal capsule. The internal capsule carries all axons emanating from the cerebral cortex and ending in thalamus, brainstem, or spinal cord. The internal capsule consists of an anterior limb, genu, and posterior limb. In addition, fibers ascending from thalamus to the cerebral cortex travel in the internal capsule. However, fibers ascending from brainstem or spinal cord to thalamus do not travel in the internal capsule. Therefore, the entire length of the internal capsule carries motor fibers, descending from motor cortex, whereas only the part closest to the corona radiata carries sensory fibers ascending from thalamus.

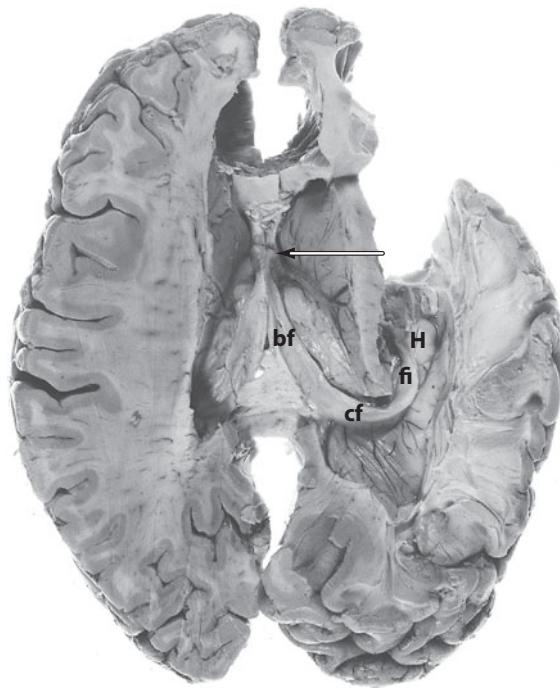
Photographs reprinted with permission from Bruni, J.E., and Montemurro, D. *Human neuroanatomy: A text, brain atlas, and laboratory dissection guide*. New York: Oxford University Press, 2009.

- The corpus callosum is the largest commissural or midline-crossing tract in the brain (see Fig. 3-8). It contains the axons of cortical neurons on one side of the brain destined for the other side of the brain.
- The fornix (Fig. 13-5) is an important tract that carries output from the hippocampus to the mammillary bodies, part of the hypothalamus, and other targets.

In this chapter, we continue our journey up the neuraxis from caudal to rostral. We start by examining the functions of the hypothalamus. We then look at thalamic function, which necessarily involves an examination of the bidirectional interactions between the thalamus and cortex. Before exploring the function of several key cortical areas and of cortex as a whole, the amygdala and basal ganglia, two important subcortical structures are described. Circuits devoted to perception, action, emotion, and abstract thought are all unique products of the forebrain. However, we start with the hypothalamus, the forebrain region that most closely resembles the brainstem in terms of the variety of functions supported.

Figure 13-5. A horizontal section through the cerebrum is shown. Anterior is up. The fornix is a large, easily recognizable tract that runs between the hippocampus and mammillary bodies. Most of the information carried in the fornix is traveling out of the hippocampal formation but some information comes into the hippocampal formation via the fornix. As fibers exit from the hippocampus (*H*), they initially form the **fimbria** (*fi*), which becomes the **crus of the fornix** (*cf*) as the axons leave the parahippocampal gyrus. Fibers of the fornix travel medially along the inside curve of the lateral ventricle. Upon reaching the midline, the fornix forms the **body of the fornix** (*bf*). At the arrow, fibers of the fornix dive ventrally between the lateral ventricles as the **columns of the fornix** which ultimately terminate in the mammillary bodies.

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THE HYPOTHALAMUS SERVES AS THE EXECUTIVE CENTER FOR REGULATING AND PROTECTING THE BODY'S PHYSIOLOGY

The variety of processes with which the hypothalamus is concerned varies from critical but unexciting functions, such as electrolyte balance, to more lofty roles, such as facilitating pair-bonding with another individual. The hypothalamus projects to and employs the pituitary, or **hypophysis**, as well as autonomic, somatomotor, and limbic pathways to effect coordinated changes in hormonal release, internal physiology, somatomotor actions, as well as emotion and motivation (Fig. 13-6). Some of the notable functions of the hypothalamus include:

- *Fluid and electrolyte balance*: ensures adequate blood volume and keeps blood osmolarity and electrolyte concentrations within narrow ranges
- *Energy*: ensures adequate energy intake through feeding and regulates energy expenditure to protect against starvation
- *Growth*: regulates the release of growth hormone from the anterior pituitary, which in turn stimulates cell growth and division
- *Thermoregulation*: maintains body temperature within a narrow temperature range appropriate to varying conditions
- *Mating and reproduction*: regulates the drive to seek a sexual partner, as well as sexual motor acts themselves; directs the hormonal environment appropriate for pregnancy and lactation; initiates and contributes to puberty

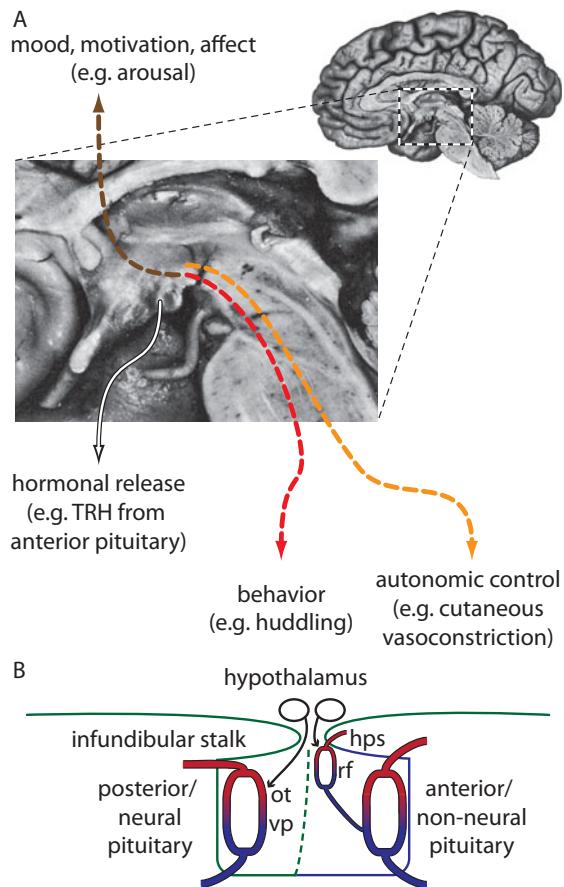


Figure 13-6. A: The hypothalamus is illustrated on a mid-sagittal section. The hypothalamus serves to maintain and protect the body's physiology by controlling hormonal release, motor behavior, autonomic function, mood, and motivation. As an example, when we walk outside on a very cold day, our hypothalamus coordinates our defense against the cold. The hypothalamus releases hormones, such as thyroid releasing hormone, which act on the pituitary to activate thyroid function and increase metabolism. The hypothalamus also sets into motion behavioral reactions, such as putting on a coat or huddling within a protected space. Autonomic reactions coordinated by the hypothalamus include cutaneous vasoconstriction, which restricts the exposure of warm blood to the cold elements. Finally, being challenged by a very cold environment arouses us, preventing us from falling asleep and motivating us to action. To accomplish these diverse goals, hypothalamus uses projections to the pituitary, the brainstem and spinal cord, and to the cortex. B: The posterior part of the pituitary is the neural portion, also termed the *neurohypophysis*, and the anterior part is a non-neural gland often called the *adenohypophysis*. The hypothalamus controls the posterior or neural pituitary via direct release of hormones, either oxytocin (*ot*) or vasopressin (*vp*) into the systemic circulation. In contrast, the hypothalamus controls release of several hormones from the anterior pituitary indirectly by releasing hormonal releasing factors (*rf*) into the hypophyseal portal system (*hps*). Endocrine cells in the anterior pituitary respond to the releasing factors to release hormones into the general circulation.

Photographs reprinted with permission from deArmond S., et al. *Structure of the human brain: A photographic atlas*. New York: Oxford University Press, 1989.

- *Circadian rhythm*: coordinates the daily rhythm of behavior, physiology, and hormone release

Although the hypothalamus is critical to maintaining the body within physiological limits, it only does so in partnership with the rest of the brain. The hypothalamus integrates information from multiple sensory modalities about the environment, both internal and external to the individual with internal motivations, memories, and action plans. Because of the wide variety of information reaching the hypothalamus, our ability to react to challenges is highly flexible. For example, we may eat when we feel both chilly and hungry but move around if we feel chilly and not particularly hungry. As with all neural function, it is context that narrows down the wide range

of meanings ascribable to any one stimulus, and which in turn dictates the hypothalamus' eventual interpretation.

Once the hypothalamus arrives at an interpretation of a situation, it directs appropriate reactions and coordinates responses of several types. For example, when a newborn suckles on the mother's breast, the neuropeptide **oxytocin** is released into the mother's hypothalamus and into the systemic circulation via the pituitary (see more below). Release of oxytocin into the circulation leads to milk letdown, while oxytocin released into the hypothalamus leads to a reduction in the emotional reaction to stressful events. In this way, mothers nurse while being biologically inclined to more easily absorb the stress of a dependent baby (see Box 13-3).

Box 13-3

POSTPARTUM MOOD DISORDERS MAY INVOLVE ALTERED LEVELS IN HYPOTHALAMIC NEUROPEPTIDES, SUCH AS OXYTOCIN AND PROLACTIN.

The period in a female's life after the birth of a child is biologically stressful. The mother must adapt to a baby's crying and needs, to her own sleep deprivation, and to radical changes in her body's physiology, while also tolerating repeated nursing. Although in modern life, some mothers have access to nannies and the like, natural selection has left us with a system evolved under conditions in which babies are wholly dependent on mother, day in and day out. Cultural challenges piggy-back upon the biological ones. Whether having her first or fifth child, a woman faces the additional stress of changing family dynamics during the already challenging postpartum period.

To promote maternal well-being, and in turn, a child's development, nature has armed mothers with ammunition against the difficulties of the postpartum period. The ammunition comes in two forms. First, contact with her baby improves a mother's mood. Second, a flood of neurochemical and hormonal changes lead to improved mood, reduced anxiety, and reduced reactivity to stress, virtually a neural version of a "chill pill." For example, oxytocin and another neuropeptide **prolactin** are both released from hypothalamic neurons and both reduce anxiety and reactivity to stress. The apparently redundant effects of the two neuropeptides likely reflect the extremely critical need for a mother to maintain a stable, upbeat mood. Imagine how helpful an upbeat attitude would be to a woman who is nursing and caring for a completely helpless baby all the time, 24-7 in the modern vernacular.

Furthermore, buoying a mother's mood and ability to cope with challenges will inevitably facilitate the child's normal and healthy development.

In a number of recently, well-publicized tragic cases, women suffering from either **postpartum depression** or **postpartum psychosis** have harmed, abandoned, or even killed their babies. Thankfully, such extreme types of **postpartum mood disorders** are rare. The most common form of postpartum mood disorder is in fact **postpartum anxiety**. Unfortunately, since plasma levels of neurotransmitters do not reflect brain levels, we know little about the neurochemistry of the postpartum period directly from women. However, we have learned a great deal about the roles of prolactin, oxytocin, and the like from findings in laboratory animals. Oxytocin, which can be administered intranasally to women, may prove to be a useful and effective treatment for some postpartum disorders. Furthermore, the ability of contact with her baby to improve a woman's mood and reduce her anxiety provides a simple method for cutting a mother's risk of developing a mood or anxiety disorder.

In contrast to our burgeoning knowledge regarding the role of the hypothalamus in postpartum maternal behavior and maternal care, we know very little about the brain and paternal care. Our lack of information is not evidence that fathers are or are not biologically inclined to provide parental or spousal care—it is simply a hole in our knowledge that we need to fill.

The hypothalamus is continuous caudally with the midbrain periaqueductal gray and together the two regions organize complex reactions to physiological challenges. The hypothalamus alone controls the pituitary and contributes to the regulation of mood and motivation. The hypothalamus and periaqueductal gray work together to coordinate somatomotor and autonomic reactions to outside threats.

THE HYPOTHALAMUS CONTROLS BOTH THE NEURAL AND THE NON-NEURAL DIVISIONS OF THE PITUITARY

The pituitary is a gland that sits outside of the central nervous system in a bony cavity called the **sella turcica**. The base of the hypothalamus connects to the pituitary via the infundibular stalk, or **median eminence**, which penetrates through the dura. The pituitary consists of two parts, which the hypothalamus controls in different ways:

- The posterior portion is the **neural pituitary** or **posterior pituitary** or **neurohypophysis**. Hypothalamic cells make and release hormones from axonal terminals in the neurohypophysis. Within the posterior pituitary, hypothalamic cells release hormones directly into the systemic circulation so that, like motoneurons, hypothalamic cells directly alter peripheral function.
- The anterior portion is the **non-neural pituitary** or **adenohypophysis**. Hypothalamic cells control the adenohypophysis through an indirect pathway involving a private circulatory system, the **hypophysial portal system**, a set of capillary beds interconnected by veins (see more below and Fig. 13-6B).

The two hormones, both of which are neuropeptides (see Chapter 7), released from the posterior pituitary are:

- Oxytocin
- Vasopressin or **antidiuretic hormone**, commonly abbreviated as **ADH**

Peripherally, oxytocin and vasopressin act as hormones to regulate fluid balance, along with a number of reproductive functions. Further, like other pituitary hormones, oxytocin and vasopressin are also released into the hypothalamus. *The release of hormones into both the hypothalamus and the general circulation allows for coordinated hormonal regulation of somatomotor, autonomic, emotional, and cognitive processes in service of complex goals such as hydration or maternal care.* For example, when an increase in plasma osmolarity is detected in the hypothalamus and afferents to the hypothalamus signal a decrease in blood pressure and a dry mouth, ADH is released into both the blood stream and the hypothalamus. Antidiuretic hormone acts on the kidneys to concentrate urine, reabsorb more water, and decrease

urine output while acting on the brain to stimulate the search for, and drinking of, fluids. In this way, the coordinated actions of ADH on body and behavior will rectify the original problem of dehydration (see Box 13-4), thus maintaining the body's physiology within acceptable limits.

The hypothalamus regulates the anterior pituitary only indirectly via the hypophysial portal system. Neurons in the hypothalamus release **hormonal releasing factors** into the hypophysial portal system:

- **Corticotropin-releasing hormone** or **CRH** leads to the release of **adrenocorticotropic hormone** or **ACTH**, which has multiple effects on the brain and body, all of which are part of the reaction to stress.
- **Thyrotropin-releasing hormone** or **TRH** increases the release of **thyroid stimulating hormone**, also termed **thyrotropin** or **TSH**. Thyrotropin stimulates the thyroid gland to increase metabolism and energy expenditure.
- TRH release also increases, whereas **dopamine** decreases **prolactin** release, which in turn stimulates milk production and modulates sexual arousal.
- **Growth hormone-releasing hormone** or **GHRH** stimulates the release of **growth hormone**, also known as **somatotropin**. **Somatostatin** inhibits the

Box 13-4

CENTRAL DIABETES INSIPIDUS RESULTS FROM A DEFICIT IN HYPOTHALAMIC VASOPRESSIN.

Antidiuretic hormone (ADH) or vasopressin is released by the hypothalamus. Normally, when the blood osmolarity increases, evidence of dehydration, ADH acts on the kidneys to increase the salt concentration of urine. This minimizes the fluid that is excreted. Without ADH, the hypothalamus cannot regulate kidney function. In the absence of even baseline levels of ADH, the kidneys work harder and more urine is voided, termed **polyuria**. Moreover, the voided urine is far more dilute than usual. Excessive voiding of dilute urine leads to insufficient hydration, marked by elevated plasma osmolarity and a feeling of thirst. The affected person drinks more than usual, termed **polydipsia**. (Note that while ADH contributes to the motivation to drink in response to thirst and dehydration, it is not the only factor. As a result, people continue to drink even without ADH.) The water ingested further dilutes the urine voided and so on. Increased voiding of dilute urine causes a further increase in plasma osmolarity, which again cannot be rectified because of the lack of ADH. This vicious cycle leads to high plasma osmolarity and low urine osmolarity, the

cardinal signs of **diabetes insipidus**. The end result is greatly increased intake and output of water as though the affected person were a *siphon*, the Greek word for which is the root of the word diabetes. The term **insipidus** reflects the insipid or tasteless water that is siphoned through in affected individuals. Note that diabetes insipidus is distinct from **diabetes mellitus**, a condition in which glucose is not appropriately processed by insulin. A major difference between the two conditions is that the urine in patients with diabetes mellitus contains elevated levels of glucose (mellitus is derived from Greek words meaning *honey sweet*), whereas the urine in patients with diabetes insipidus does not.

Diabetes insipidus resulting from dysfunction in hypothalamic or pituitary release of ADH is termed **central** or **neurogenic** and can result from a tumor in the pituitary or hypothalamus. Iatrogenic cases of central diabetes insipidus can also be the unintentional result of surgical removal of a pituitary tumor. Diabetes insipidus can be a reversible condition, in which case it does not require lifelong treatment as in the case of type 1 diabetes mellitus.

release of growth hormone which, as the name suggests, increases bone and muscle growth.

- Gonadotropin-releasing hormone or GnRH stimulates the release of luteinizing hormone, or LH, which stimulates ovulation in women and testosterone production in men.
- GnRH also stimulates the release of follicular-stimulating hormone, or FSH, which is critical to reproductive function across the life cycle in both women and men.

Secretory cells in the anterior pituitary respond to hypothalamic releasing factors by releasing hormones, which in turn act on glands and other tissues such as the gonads. The effects of hormones released by the anterior pituitary exert effects on growth, metabolism, reproductive function, and the generalized stress reaction (see Box 13-5).

As an example of the hypothalamic influence on the adenohypophysis, consider the generalized stress reaction. In response to CRH released into the hypophysial portal system, the adenohypophysis releases ACTH. Adrenocorticotrophic hormone in turn acts on the adrenal gland to stimulate release of corticosteroids, principally

Box 13-5

PITUITARY TUMORS CAN IMPAIR VISION AND CAN ALSO CAUSE SYMPTOMS DUE TO HORMONE OVERPRODUCTION.

Pituitary tumors are relatively common neoplastic growths, typically benign, in the anterior pituitary. Most people with such pituitary adenomas never experience any adverse symptoms. Pituitary tumors cause symptoms in one of two ways. First, some pituitary adenomas cause excess secretion of one or more adenohypophyseal hormones, most typically prolactin, growth hormone, or adrenocorticotrophic hormone (ACTH), which then produce symptoms that lead the affected individual to seek medical advice. For example, excess secretion of growth hormone in an adult causes excessive and painful growth, termed **acromegaly**. Visible signs of acromegaly include protrusive growth in the hands, brow, and jaw. If excess amounts of growth hormone are secreted in a prepubertal child, **gigantism** will result if the condition is not treated.

The second way in which pituitary adenomas produce symptoms is by impinging on neighboring structures. Because of their space-occupying nature, pituitary adenomas can compress and consequently impair neighboring regions, including the posterior pituitary, hypothalamus, and optic chiasm.

For example, a pituitary tumor that presses on the hypothalamic connection to the neurohypophysis is likely to cause diabetes insipidus.

The most common presenting symptom of a pituitary tumor is blurred vision due to compression of the optic chiasm. This is because the pituitary sits just below and behind the optic chiasm within a bony cavity that prevents expansion in any direction but up and to the front. The optic chiasm carries visual information from the temporal half of each visual field to the contralateral lateral geniculate nucleus (Fig. 10-5). Therefore, when a pituitary tumor presses on the optic chiasm, the temporal parts of the visual world become blurry or obscured altogether. The inability to see the temporal hemifield from either eye is termed **bitemporal hemianopia** and is a common symptom of space-occupying pituitary adenomas.

Although some secreting pituitary tumors can be shrunk using medications targeting the oversecreting cells, many patients undergo **trans-sphenoidal**, meaning via an approach through the nose, surgery, which is usually successful.

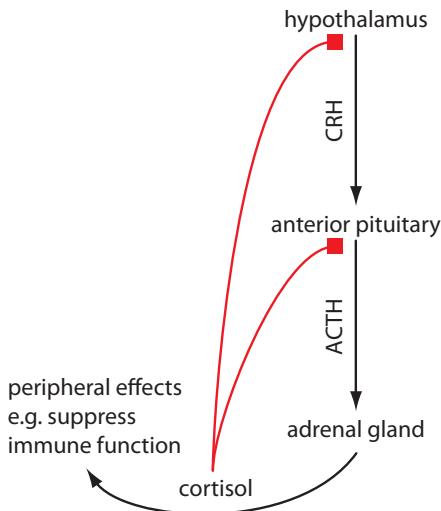


Figure 13-7. The hypothalamic-pituitary-adrenal axis refers to the connection from the brain to the adrenal gland. During stressful conditions, stress-activated neurons in the hypothalamus release corticotropin releasing hormone (CRH), which evokes the release of adrenocorticotrophic hormone (ACTH) from the adenohypophysis or anterior pituitary. ACTH acts on the adrenal gland to release cortisol into the systemic circulation. Cortisol has diverse effects on the body, such as increasing gastric acid secretions and suppressing immune function. Cortisol exerts inhibitory feedback control (red ■ symbols) on both CRH release from the hypothalamus and ACTH release from the adenohypophysis.

cortisol, often referred to as the “stress hormone.” The pathway from the hypothalamus to the anterior pituitary and then to the adrenal gland is termed the **hypothalamic-pituitary-adrenal axis**, typically abbreviated as the **HPA axis** (Fig. 13-7). Cortisol provides a hormonal jolt, mobilizing the body’s resources for movement and action while shutting down immunological function. Cortisol also inhibits both ACTH release from the pituitary and CRH release from the hypothalamus, thus providing a termination signal and preventing cortisol release from accelerating out of control. It should be noted that stress reactions are necessary for normal physiological function. Although too much and too little cortisol are both problematic, too little is a far more serious and potentially fatal condition (see Box 13-6).

Box 13-6

OVERPRODUCTION OF CORTISOL CAUSES SEVERE WEIGHT GAIN AND OTHER PROBLEMS, WHEREAS CORTISOL INSUFFICIENCY CAN BE FATAL.

Cushing’s disease occurs when a pituitary adenoma causes overproduction of adrenocorticotrophic hormone (ACTH) which in turn leads to excess cortisol production. When the same end result—excessive cortisol—results from an adrenal tumor, intake of a steroid medication, or other cause, it is termed **Cushing’s syndrome**. High levels of cortisol cause severe weight gain, particularly in the face and trunk. Treatments for Cushing’s syndrome and disease are aimed at removing the source of cortisol production and surgical removal of the pituitary adenoma, respectively.

Although modern vernacular views stress as a negative and the absence of stress as desirable, an insufficient amount of the stress hormone cortisol, a condition known as **Addison’s disease**, is potentially fatal. Without cortisol, individuals are fatigued, have little appetite, and are hypotensive.

Most importantly, people with Addison’s disease cannot react appropriately to homeostatic challenges. As a result, stressors can trigger a potentially fatal **Addisonian crisis** which is marked by sudden back and leg pain, low blood pressure, vomiting, and unconsciousness. Most cases of Addison’s disease stem from the autoimmune destruction of adrenal tissue and are treated by supplying drugs that substitute for the missing adrenal hormones.

Contrasting Addison’s disease with Cushing’s syndrome tells us something important. The concentration of hormones, such as cortisol, needs to be just right, neither too high nor too low. Furthermore, the appropriate amount of cortisol is different across varying conditions. We need more cortisol during periods of stress, and without it, our body cannot rise to the challenges presented.

SENSORY INFORMATION TRANSFERS WITHIN THE THALAMUS TO REACH THE CORTEX

Sensory input from the eyes, ears, mouth, head and body cannot reach the cerebral cortex without first synapsing in the thalamus (see Box 13-7). For example, consider that a snowball hits you in the face. Information about this cold and icy turn of events will reach the somatosensory cortex only after a layover, meaning a synapse, in the somatosensory part of the thalamus. The most important sensory nuclei of the thalamus are:

- The lateral geniculate nucleus contains neurons that receive visual input from the retina and provide input to primary visual cortex (see Table 13-1).
- The medial geniculate nucleus contains neurons that receive auditory input from the inferior colliculus and provide input to primary auditory cortex (see Table 13-1).
- Neurons in the **ventral posterolateral nucleus** receive somatosensory input from the body, from both the dorsal column-medial lemniscus and spinothalamic systems, and provide input to primary somatosensory cortex (see Table 13-1).
- Neurons in the **ventral posteromedial nucleus** receive somatosensory input from the face and oral cavity via **trigeminothalamic tracts**. These thalamic neurons also receive gustatory input. Somatosensory information is sent to the appropriate region of primary somatosensory cortex, while gustatory information is sent to the gustatory cortex in the insula, the region of cortex tucked deep within the Sylvian fissure (see Table 13-1).

Box 13-7

AT LEAST SOME CHEMOSENSORY INPUT REACHES CORTEX DIRECTLY WITHOUT A SYNAPSE IN THE THALAMUS.

Olfactory receptor neurons in the nose cross the cribriform plate to synapse in the olfactory bulb (see Chapter 10). Since the olfactory bulb is part of the cerebral cortex, this means that olfactory receptor neurons project directly to cortex without a stop in thalamus. Thus, olfactory pathways appear to violate the rule that all sensory input synapses in thalamus before reaching cortex. However, the olfactory bulb is different from other regions of sensory cortex

and in fact, functions much as thalamus does. The same modulatory inputs from the brainstem that project to the thalamus also reach the olfactory bulb. Within the bulb, input about odorants is blocked, facilitated, or otherwise modulated, with the effect that the meaning of olfactory nerve input can be modified. In this way, the olfactory bulb functions in olfaction much as the thalamus functions in other sensory systems.

TABLE 13-1. EACH OF THE SENSORY PATHWAYS ILLUSTRATED HERE CONTAINS AT LEAST FOUR NEURONS

	SOMATOSENSATION					
	VISION	HEARING	DC-ML	STT	V	TASTE
Sensory transduction cell	Retinal photoreceptor (rod or cone)	Cochlear hair cell	Dorsal root ganglion cell or sensory cell (e.g. Merkel cell)	Dorsal root ganglion cell	Trigeminal ganglion cell or sensory cell (e.g. Merkel cell)	Taste bud cell
Primary sensory afferent	n.a.	Spiral ganglion	Dorsal root ganglion cell	Dorsal root ganglion cell	Trigeminal ganglion cell	Cranial ganglion cell (e.g. geniculate ganglion)
Thalamic projection neuron	Retinal ganglion cell	Inferior colliculus neuron	Dorsal column nuclear cell	Dorsal horn cell	Main sensory / Spinal trigeminal nuclear cells	not known
Location of thalamic neuron	Lateral geniculate nucleus	Medial geniculate nucleus		Ventral posterolateral nucleus	Ventral posteromedial nucleus	
Primary cortical target	Primary visual cortex	Primary auditory cortex			Primary somatosensory cortex	Primary gustatory cortex
Function	Visual perception	Auditory perception		Somatosensory perception from the body and face		Taste perception

The pathways start with a cell that transduces, or converts, sensory input into an electrical signal and includes a neuron that projects to the thalamus, a thalamic neuron, and a cortical neuron. In the cases of some somatosensory modalities, the same dorsal root or trigeminal ganglion cell transduces sensory input and serves as the primary afferent. In other cases, such as audition and taste, the transducing cell and the primary afferent are two different cells. One or more cells intervene between the primary afferent and the thalamic projection neuron.

Visual, auditory, somatosensory, and gustatory inputs all synapse in the thalamus en route to the cerebral cortex. Ventral posterior nuclei in the thalamus and primary somatosensory cortex perform double duty. Touch and pain pathways from the body both use the ventral posterolateral nucleus while trigeminal somatosensation and taste share the ventral posteromedial nucleus. Somatosensory pathways from all modalities and from both face and body reach the primary somatosensory cortex.

For most sensory information, the thalamus is a requisite way-station to get to cerebral cortex. The synapse within the thalamus is the penultimate step for the two long sensory tracts that we have followed for several chapters now. Both the spinothalamic tract and the medial lemniscus synapse within the ventral posterolateral nucleus, which along with the ventral posteromedial nucleus is often termed the **ventrobasal complex**. Thalamic neurons then carry somatosensory information, concerning pain and temperature as well as proprioception, touch, pressure, and vibration, to the primary somatosensory cortex. A lesion to the ventrobasal nucleus will result in positive signs, such as pain or dysesthesia, as well as a deficit in contralateral somatosensation (see Box 13-8).

Other sensory nuclei of the thalamus play similar roles to that of the ventral posterolateral nucleus. For example, damage to the lateral geniculate nucleus impairs contralateral visual perception, rendering the visual world contralateral to the lesion, termed the contralateral visual hemifield (see Chapter 10), invisible to either eye (see more below). However, unilateral damage to the medial geniculate nucleus does not impact hearing (see Box 13-9).

VENTRAL POSTERIOR THALAMIC DAMAGE CAN PRODUCE A CENTRAL PAIN SYNDROME.

Damage to the ventrobasal complex or nearby posterior thalamic regions that interrupts the spinothalamic tract can cause a debilitating chronic pain condition called **central post-stroke pain**. This syndrome was previously known as **thalamic pain syndrome** or **Dejerine-Roussy disease** until it became clear that strokes outside of the thalamus could also produce a similar syndrome of central pain. Central post-stroke pain affects up to 10% of stroke victims and is associated with lesions to ascending pain pathways. Central post-stroke pain is a form of **neuropathic pain**, which means that no physical

stimulus is present and responsible for the pain sensation (see more in Chapter 18). Instead, the pain results from errant signaling in the nervous system. Patients typically perceive a sensation of burning, searing pain contralaterally. Central post-stroke pain is typically treated with either tricyclic antidepressants or anticonvulsants. These drugs are used at doses that have little effect on depression or seizures and are thought to decrease pain by blocking burst firing in pain-responsive neurons. Narcotics are typically not used to treat central post-stroke pain.

THALAMIC DAMAGE RARELY CAUSES DEFICITS IN HEARING OR TASTE.

Since the medial geniculate nucleus receives auditory input from both ears, unilateral damage to the medial geniculate does not cause noticeable damage to hearing function. Similarly, unilateral lesions in thalamus and elsewhere do not impair taste, probably because taste is bilaterally redundant. In fact, a loss of taste, termed **ageusia**, or an impairment of taste (**hypogeusia** is a partial loss of taste and **dysgeusia** refers to an abnormal sense of taste) occurs, but is rare. The rare cases of taste impairment that occur are almost always due to peripheral damage to the oral cavity or to cranial nerves carrying gustatory information.

SENSORY THALAMUS IS NOT JUST A RELAY STATION

Sensory thalamus is insinuated between the lowest and highest level of central sensory processing. As a rule, sensory information reaches from the periphery to the cortex in a stereotyped manner:

stimulus → primary sensory neuron → ≥1 secondary sensory neurons → **thalamus** → primary sensory cortex

For vision, the basic pathway is:

light → retinal photoreceptor → → retinal ganglion cell → **lateral geniculate nucleus** → primary visual cortex

Despite there being two tracts carrying somatosensory input from the body, somatosensory pathways have a similar organization:

touch, vibration, proprioception → primary somatosensory afferent → dorsal column nucleus → **ventral posterolateral nucleus** → primary somatosensory cortex

pain and temperature → primary somatosensory afferent → spinal dorsal horn → → **ventral posterolateral nucleus** → primary somatosensory cortex

One way to view the synapse in thalamus is that it provides a “boost” or a “leg-up,” a metabolic and nutritive support for the long journey from here to there. Yet,

we know that many axons, including dorsal column axons and spinothalamic tract axons, can stretch a meter or more in some individuals. Therefore, it is unlikely that sensory pathways synapse in the thalamus because cortex is too far away for a direct, single axon projection. Rather, as this line of reasoning suggests, the thalamus serves as far more than a relay station. To appreciate the true contributions contributed by the thalamus, consider vision. The input from retinal ganglion cells to lateral geniculate neurons comprises well under 10% of the entire input to these thalamic cells. Similarly, ventrobasal complex neurons receive only a small proportion of their input from the medial lemniscus or spinothalamic tract (Fig. 13-8).

Thalamic neurons that project to the cortex are called **thalamocortical projection cells**. As described above, only a minority of the synapses on thalamocortical projection cells arise from **lemniscal** pathways, which are those, such as the medial lemniscus, that carry sensory input. Instead, most synaptic input to thalamocortical projection cells in thalamic sensory nuclei arises from one of three sources:

- **Thalamic neurons:** Local neurons in the same thalamic nucleus as well as neurons in the surrounding **thalamic reticular nucleus** are sources of inhibitory input. Such inhibitory input can sharpen the distinction between stimulated areas and areas not stimulated, enhancing “edge” detection.
- **Brainstem nuclei:** Neurons in select brainstem nuclei release neuromodulators, such as serotonin and norepinephrine, which modulate the sensitivity of

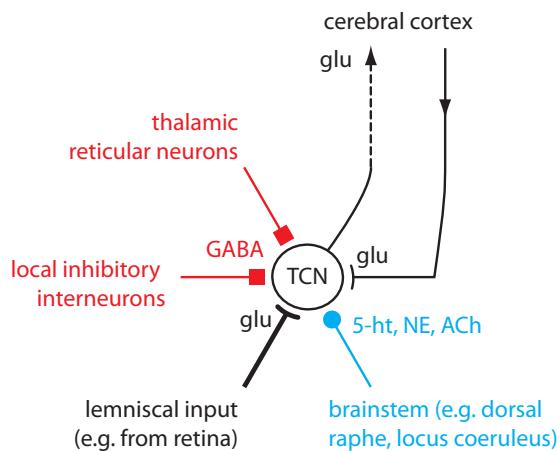


Figure 13-8. Thalamocortical projection neurons receive an enormous number of inputs, only a minority of which arise from lemniscal pathways. Thus, in terms of **number of synapses**, nonlemniscal inputs to thalamocortical projection neurons dominate over lemniscal inputs. Nonlemniscal inputs arise from a variety of brainstem nuclei, cortex, the thalamic reticular nucleus, and from local inhibitory interneurons. The corticothalamic input to thalamocortical projection neurons arises primarily from the same part of cortex to which the thalamic neuron projects. Lemniscal inputs and feedback from cortex to the thalamocortical projection neuron use the neurotransmitter glutamate (black). Therefore, input from cortex provides **excitatory feedback**. The inputs from local interneurons and from the thalamic reticular nucleus are GABAergic (red) and inhibitory. As both local interneurons and thalamic reticular neurons receive excitatory inputs from lemniscal inputs and/or thalamocortical projection neurons, the GABAergic inputs onto thalamocortical projection neurons from these cells provides **inhibitory feedback**. Inputs from the brainstem arise from neurons in nuclei including the **dorsal raphe** and **locus coeruleus**, which use a monoamine as neurotransmitter. Inputs from brainstem therefore release a variety of neurotransmitters (blue) including serotonin (5-HT), norepinephrine (NE), and acetylcholine (ACh). Although inputs from nonlemniscal sources dominate, lemniscal input onto thalamocortical neurons carry far more weight than nonlemniscal inputs. As a consequence, the discharge of thalamocortical neurons most closely resembles firing in lemniscal pathways.

thalamic neurons to sensory inputs. The neuromodulatory substances released at any one moment depend on **behavioral state**. In this way, different complements of modulatory substances are released during wakefulness, non-rapid eye movement (REM) sleep, REM sleep, vigilance, and so on.

- **Cerebral cortex:** Cortical regions that receive thalamocortical input send corticothalamic projections back to thalamus. For example, primary visual cortex projects to the lateral geniculate nucleus. Such projections allow cortex to influence our perceptions at an early point in sensory pathways.

Even though secondary sensory neurons provide only a small proportion of the input to sensory thalamic nuclei, this input has a stronger and more reliable influence than the effect of any single synapse from the brainstem or cortex. To paraphrase George Orwell, some synapses “are more equal than others.” Nonetheless, the picture that emerges is that *sensory input arising from the world is one component but certainly not the sum total of information that the thalamus passes on to the cortex*. The large number of inputs to sensory thalamic neurons from areas of the brain other than pathways bringing in sensory input from the periphery reflects the fact that we *interpret* rather than faithfully record the sensory world (see Chapter 15).

SENSORY THALAMUS SERVES AS INTERPRETER, GATE-KEEPER, AND SPOTLIGHT OPERATOR

The requisite synapse in the thalamus allows sensory input to be translated into a message that is interpretable by the cortex. The thalamus can close the gate on sensory information, as occurs during sleep. The thalamus also plays a key role in setting attention to particular parts or features of the sensory world and to allowing expectation to either anticipate or color sensory events.

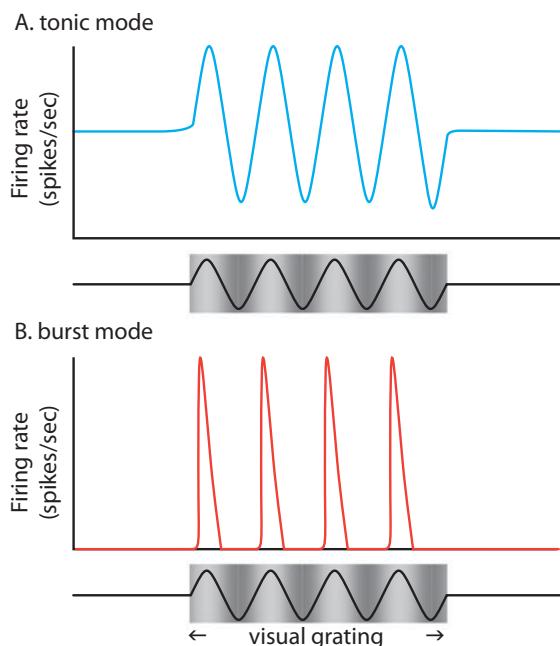
Key to the thalamus’ role in interpreting and modulating sensory input to the cortex is a particular physiological characteristic of thalamocortical projection cells. Thalamocortical neurons are often termed “relay cells” but this is a misnomer. In fact, thalamocortical projection cells operate in one of two modes, only one of which is relay-like in nature:

- In **relay mode**, thalamic neurons faithfully pass on the message that they receive from secondary sensory neurons (Fig. 13-9A). The sequence of action potentials sent by the thalamic neuron matches nearly exactly the sequence of action potentials received by the thalamic neuron in a one-to-one fashion.
- In **burst mode**, thalamic neurons fire a batch of action potentials upon receipt of an action potential (Fig. 13-9B). By transforming one action potential into many action potentials, a thalamic neuron in burst mode can serve to “awaken” the cortex or to increase attention to a particular stimulus feature.

Thalamocortical projection cells operate in either relay or burst mode depending on inputs from brainstem nuclei that release neuromodulators (Fig. 13-8). The neuromodulators released within thalamus vary across behavioral states such as wake and sleep. Consequently, thalamic firing differs across behavioral states.

As an example of how the thalamus functions, consider the consequences of a tap on the shoulder during wake or sleep. During wakefulness, a tap will activate primary afferents that will ascend through the dorsal columns to synapse in the nucleus cuneatus. Neurons in nucleus cuneatus will send axons across the midline into the medial lemniscus. These axons ultimately synapse in the ventral posterolateral nucleus of the thalamus. During wakefulness, neurons in the ventral posterolateral nucleus are in the tonic mode (Fig. 13-9A). Therefore, virtually the same message that thalamic neurons receive from the dorsal column nucleus is sent to the somatosensory cortex when we are awake. The result of this entire pathway is that we perceive the incident tap. Now, consider that the same tap occurs during non-REM sleep rather than during wakefulness. The tap still activates primary afferents and the resulting message still reaches the thalamus. However, during sleep, thalamic neurons are bathed in a complement of neuromodulators that puts them into burst mode (Fig. 13-9B). A light tap may elicit *no response at all* in a ventral posterolateral thalamic neuron. However, a stronger tap may elicit a burst of activity in thalamocortical projection neurons. When it does, the result is strong activation of the somatosensory cortex producing a perception *more notable for startle than for any of the sensory characteristics of the tap*—location, duration, intensity. Sensory features of a stimulus are poorly represented in both thalamus and cortex when thalamic neurons are in burst mode. On the other hand, activation of thalamic neurons in burst mode increases detection of sensory stimuli and may radically shift the behavioral state toward greater arousal and vigilance.

Figure 13-9. Thalamocortical projection neurons have two different modes of firing. In response to a sinusoidal grating of stripes (visual grating), lateral geniculate neurons respond differently when in tonic mode (A) or in burst mode (B). When in the tonic mode of firing, thalamic neurons faithfully represent the input that they receive. In contrast, when in burst mode, thalamocortical projection neurons burst in response to each stimulus cycle. In the absence of stimulation (flat lines on either side of the visual grating), neurons in tonic mode fire at a relatively steady rate of discharge whereas neurons in burst mode are hyperpolarized and do not fire.
Modified from Sherman, S.M. Tonic and burst firing: dual modes of thalamocortical relay. *Trends Neurosci* 24:122–126, 2001, with permission of the publisher, Elsevier.



It is interesting to note how that tap on the shoulder is processed during REM sleep (see Chapter 27). During REM sleep, the thalamus is bathed in a neuromodulator “soup” that resembles that during wakefulness and consequently, thalamic cells tend to be in relay mode. Thus, when the phone rings while a person is in REM sleep, information about the phone ringing reaches the cerebral cortex. However, during REM sleep, we are in a state that renders muscle contraction very unlikely, a kind of reversible paralysis. Therefore, the person in REM is very unlikely to pick up and answer the phone. Instead, that person may incorporate the ringing into a dream. By similar mechanisms, many of us incorporate actual events, such as a car alarm or a barking dog, into our dreams.

THE CEREBRAL CORTEX USES INPUT FROM THALAMUS TO MAP THE OUTSIDE WORLD

Thalamocortical projection neurons contact cortical neurons that are clustered together so that cortical neurons in **columns** stretching from the pia to the white matter share functional properties. Neurons in neighboring parts of thalamus project to neighboring parts of cortex. For example, somatosensory stimulation of adjacent parts of the cutaneous surface, the skin, excites neurons in adjacent parts of thalamus and in turn, in adjacent bits of cortex. In this way, the external world is *mapped* within thalamus and then onto sensory regions of cortex. In the case of somatosensation, the topographic representation of the body across cortical columns is an example of **somatotopy**. In the case of vision, the systematic mapping of the visual field across primary visual cortex is termed **retinotopy** (see Fig. 10-5). Since maps in the visual field and in the retina are simply inverses of each other, the map present in the visual cortex is as representative of *visual field* topography as it is of *retinal* topography.

In sensory systems, some parts of the sensory world are more important than others and thus are represented by larger areas of neural tissue. For example, representation of the central 5 degrees of the visual field occupies more than half of primary visual cortex, whereas the peripheral 70 degrees on either side is represented in the remainder of the primary visual cortex. Similarly, in the somatosensory system, neurons receiving input regarding the fingertips and lips occupy far more territory than neurons that respond to stimulation anywhere on the trunk (Fig. 13-10). Clearly, the trunk contains far more surface area than do the fingertips, but, more importantly, it is far less sensitive to somatosensory stimulation than are the fingertips (see Box 13-10).

A similarly skewed representation of the periphery occurs in primary motor cortex where the map of the body is termed a **homunculus** (Fig. 13-10). Far more cortex is involved in controlling muscles capable of fine movements than in controlling muscles that are only capable of poorly controlled, ballistic movements. Therefore, the brain over-represents muscles of the hand, lips, and tongue, which produce the most articulated movements and under-represents muscles of the trunk, arms,

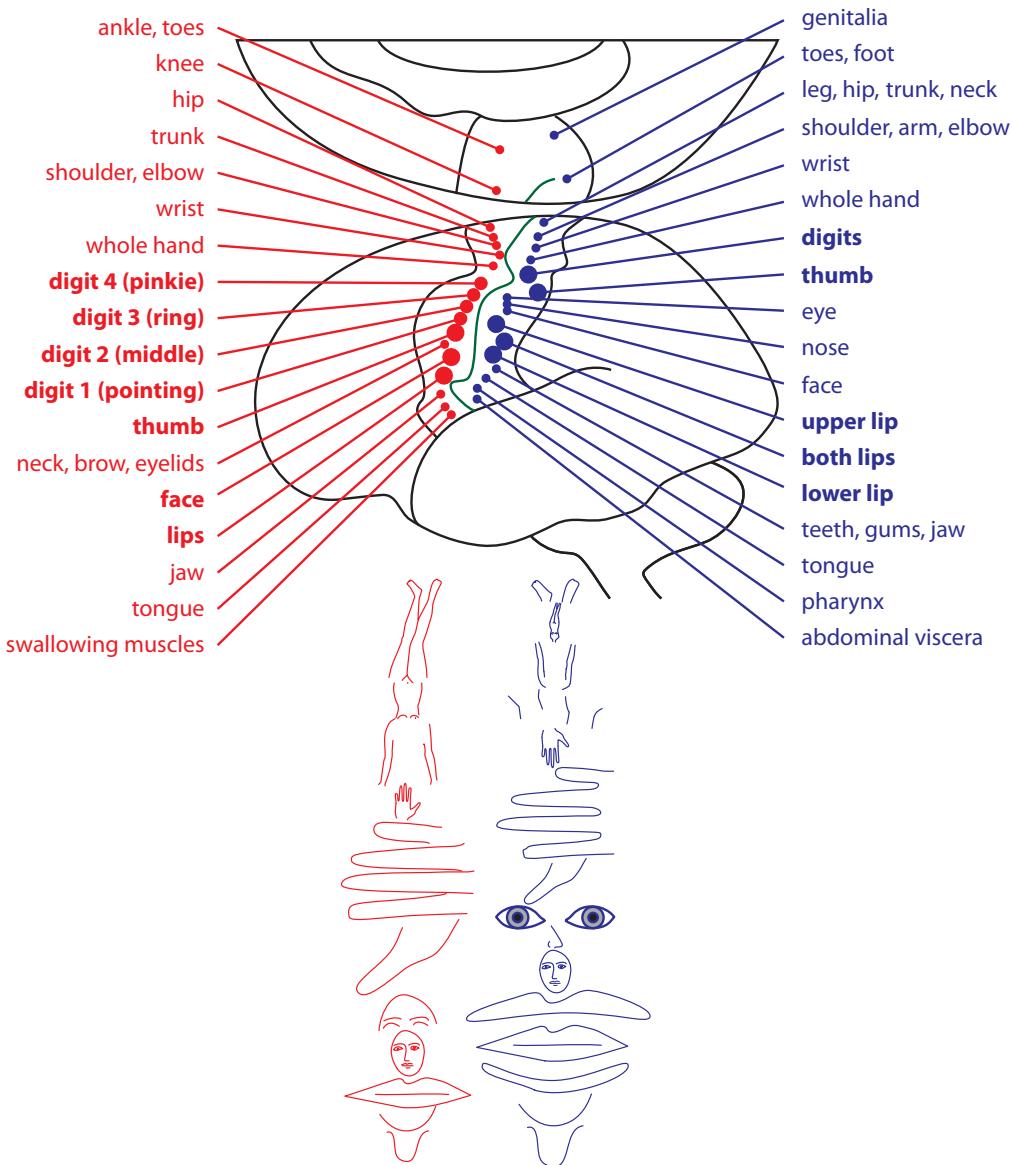


Figure 13-10. The somatotopy in primary somatosensory and motor cortices is illustrated. The lateral (bottom) and medial (top) surfaces of the brain are illustrated, with anterior toward the left. The medial surface is unfolded so that dorsal is down. In both primary somatosensory (blue) and motor (red) cortices, small regions of the body, such as the lips and hands, are represented by large regions of cortex, whereas large body parts, such as the trunk, are represented by far smaller areas of cortex. In addition, in both cortices, the most sacral regions are represented by neurons on the medial wall of the hemisphere. Moving toward the shoulders, body parts are represented by neurons in progressively more lateral regions of cortex. Areas innervated by cranial nerves, such as the face, oral cavity, upper airway, and viscera, are represented most laterally in sensorimotor cortex, with the top of the face represented most medially and the jaw and upper airway most laterally. Note that because of the curvature of the cortex, medial regions of cortex are also dorsal and lateral regions are also ventral. Both the somatosensory and motor maps are fractionated, meaning that there are jumps or discontinuities between the regions of the body represented by neighboring cortical areas. Furthermore, the maps contain multiple representations of some body parts areas. For example, the digits are represented within a hand area, as well as within an area devoted to each digit. Within somatosensory cortex, the lips are represented individually, together, and as part of the face. The homunculi in somatosensory and motor cortices differ in several regards. The greatest neural territory of motor cortex is devoted to regions of the body that support the most complex voluntary movements. The greatest neural territory of somatosensory cortex is devoted to regions with the highest tactile sensitivity (see Box 13-6). Regions such as the hands and lips are over-represented in both cortices. Yet, other areas are larger in one primary cortex region or the other. For example, a very small area of somatosensory cortex contains neurons that represent the legs, hip, trunk and neck, body parts that are represented by a territory in motor cortex several times larger. Conversely, body parts, such as the nose, teeth, and gums, are mapped in somatosensory cortex but are not represented at all in motor cortex for the simple reason that these parts are not moveable.

Box 13-10

TACTILE SENSITIVITY VARIES ACROSS THE BODY SURFACE.

A common measure of tactile sensitivity is **two-point discrimination**. You can easily measure two-point discrimination with a consenting adult. First ask your partner to look away. Then take two pencils or two stir sticks or two pointed objects of any type and place either one or both on the skin of your willing partner. Ask if your partner perceives one or two points. Stimulating closely spaced points in regions of low tactile sensitivity, for example the trunk, will be perceived as only one point of contact. In order to detect that two separate points have been contacted, the two points would have to be relatively far apart. In contrast, two points placed on regions of high tactile sensitivity, regions such as the lips or fingertips, are rarely interpreted as one point.

Box 13-11

COGNITION REFERS TO ALL MENTAL PROCESSES.

Cognition is a term that includes all mental processes. Perception, motor planning, thought, emotion, and executive function are all part of cognition. The components of cognition are each supported, either in part or wholly, by the cerebral cortex. Thus, one can view cognition as the total output of the cerebral cortex.

and legs, which produce far grosser movements. Similar but not identical topographic exaggerations mark somatosensory and motor cortices, so that the sensory and motor homunculi are similar but different.

The over-representation of some information and under-representation of other information reflects the *interpretative nature of brain function*. As discussed in Chapter 1, the brain does not faithfully and objectively record the external world as does a camera, a tape recorder, or a gas chromatograph. Nor does the brain give equal weight to all outputs as does a wind-up toy. Instead the brain infers what the outside world means for the brain's owner, ignoring inconsequential stimuli and accentuating salient features of the world. Then, the brain initiates the output reactions it deems most pressing in light of its interpretation of the most salient inputs.

THE CEREBRAL CORTEX BOTH RECEIVES AND INFLUENCES INFORMATION FROM THALAMUS

Neighboring cortical neurons receive and process information from thalamus in groups. Collections of cells that preferentially communicate with each other in patterned ways form functional **circuits**. The consequence of cortical circuits is **cognition**: perceptions, thoughts, emotions, and the initiation of actions (see Box 13-11). Different regions of the brain give rise to different components of cognition. For example, activity in a particular circuit in somatosensory cortex may result in the perception of touch, whereas activity in motor cortex may result in an action and so on.

Cortical circuits show similar activity patterns “spontaneously” and in response to thalamic input (see Box 13-12). This is a remarkable finding as it means that circuits are primed to certain activity patterns, perhaps by previous experiences, and that those patterns occur either in response to thalamic input or spontaneously without a precipitating event. Taking this idea one step further, we conclude that *the perceptions, thoughts, emotions, or actions consequent to cortical circuit activity can occur with or without a precipitating stimulus*. This provides a framework by which to understand how dreams and hallucinations can be difficult to distinguish from reality (see Box 13-13).

Recall from above that the cerebral cortex projects back to the part of thalamus from which it also receives input (Fig. 13-8). Through these corticothalamic projections, the output of cortical circuits reaches thalamus. In this way, information about expectation, attention, and the like can influence thalamic processing of secondary sensory input. *Thalamocortical firing, which is changed by cortical input, reaches cortex and is indistinguishable from thalamocortical firing that was not changed by cortical input*: both “feel” like the real deal, a true representation of the outside world. Such a scenario lends neural credibility to the idea of

Box 13-12

"SPONTANEOUS" IS A TERM THAT MAY REFLECT OUR IGNORANCE.

The word "spontaneous" describes activity or behavior that occurs without any obvious preceding stimulus. Yet, just because we fail to discern a "reason" for the activity does not mean that no preceding event caused the activity. Consider that you are sitting and chatting with others and then you stand up and start walking to the kitchen. Your movement toward the kitchen is not precipitated by any request such as "Could you please come to the kitchen?" or "Gee wouldn't it be nice to have a snack right now?" and thus appears, to others, as "spontaneous." However, another possibility is that your stomach grumbled and you became aware of being hungry. In the case of neuronal firing, we do not

have the luxury of being able to ask the neuron why it fired, as we can ask each other or ourselves why we moved to the kitchen. Therefore, we tend to label activity and behavior "spontaneous" when the precipitating reason for neuronal activity or behavior is not clearly evident. A cortical circuit that begins to fire "out of the blue" may in fact be responding to activity elsewhere in the brain. Similarly, an original thought that occurs to us "out of the blue" may in fact be a response, at some delay, to a previous event. In sum, spontaneous is a term of great convenience but one which should be used with full awareness of its potential inaccuracy.

Box 13-13

HALLUCINATIONS MAY RESULT FROM SPONTANEOUSLY OCCURRING PATTERNED ACTIVITY IN CORTICAL CIRCUITS.

Consider a pattern of activity in a cortical circuit that results in the perception of your mother's face. If that pattern of activity occurs spontaneously in your brain, then you will perceive your mom's face even if she is nowhere near you. In this way, spontaneously occurring cortical circuit activity may produce **hallucinations**. Even in the absence of a frank hallucination, preset patterns of cortical activity may transform an actual input into an expected input. When you arrive at your job, you readily perceive a coworker's face, even if most of her face is hidden from you or is covered up by winter gear. However, if you see that same face outside of the *context* of your work, you have difficulty identifying the face.

We can speculate that expectation is reflected by the spontaneous activity present in a cortical circuit. Although that activity may not be sufficient to elicit a hallucinatory perception, it may mean that less stimulus-driven activity is needed to reach the threshold for perception. Using this framework, we can imagine that, when at work, activity due to expectation and activity due to the actual stimulus summate to produce perception. However, in the absence of expectation, activity due to the stimulus alone, activity driven solely by thalamic input, is insufficient to trigger a perception. Just as expectation influences perception, it may also influence thoughts, actions, and emotions.

“seeing what you want to see.” Imbuing perception with expectation is just one of many potential, and as of yet largely unexplored, ways in which cortical circuits may influence thalamic processing.

THALAMIC NUCLEI EXCHANGE PROJECTIONS WITH CEREBRAL CORTEX TO CONTRIBUTE TO SENSORY, MOTOR, AND LIMBIC FUNCTION

By now, the reader understands that specific thalamic nuclei translate sensory information into a form that is comprehensible by the cerebral cortex. Moreover, the cortex “talks back” to thalamus. A cortical area that receives input from thalamus also sends projections back to thalamus.

In addition to the thalamocortical circuits involved in perception listed in Table 13-1, the **ventral anterior** and **ventral lateral nuclei** translate motor information into a form used by motor areas of cortex (see Table 13-2). The ventral anterior and ventral lateral nuclei receive modulatory information related to movement, largely from the basal ganglia and the cerebellum, and send it on to motor areas of cortex. The anterior nucleus of the thalamus receives input from the hippocampus and mammillary bodies related to learning and memory and projects to cingulate cortex, part of the limbic system (see Table 13-2 and Box 13-2). The **mediodorsal nucleus** receives input from the cingulate gyrus and prefrontal cortex and projects back to the prefrontal cortex to support executive function. Although serving cognitive functions other than sensory perception, the way that these thalamic nuclei operate is thought to be analogous to the way that the sensory thalamic nuclei work (see Table 13-2). In sum, thalamus appears to contribute a *method of processing* to the circuits that it participates in. It is as though the brain designed a clever computer chip, capable of transforming information in some particular way. The brain then uses this clever chip to transform data of all types and from multiple sources for use by the cerebral cortex.

TABLE 13-2. THE CONNECTIONS AND FUNCTION OF THREE THALAMIC NUCLEI THAT PROCESS INFORMATION RELATED TO MOTOR, LIMBIC, AND EXECUTIVE FUNCTION ARE LISTED

THALAMIC NUCLEUS	CORTICAL AREA TARGETED BY THALAMIC NUCLEUS	INPUT TO THALAMIC NUCLEUS	FUNCTION
Anterior nucleus	Cingulate gyrus	Mammillary bodies, hippocampus	Learning and memory
Ventral anterior and ventral lateral nuclei	Primary motor cortex and prefrontal motor areas	Cerebellum and basal ganglia	Motor function and planning
Mediodorsal nucleus	Prefrontal cortex	Prefrontal cortex, cingulate gyrus	Executive function and emotion

THE AMYGDALA IS CRITICAL TO EXPRESSING AND INTERPRETING FEAR AND FOR REMEMBERING EMOTIONAL EVENTS

The amygdala is a subcortical structure, located just deep to the cerebral cortex at the anterior pole of the medial temporal lobe (Fig. 13-3C). One intact amygdala appears to suffice for normal functioning as patients with unilateral damage to the amygdala do not show neuropsychological changes. Our initial understanding of amygdala function stems from lesion studies on macaque monkeys that suggested that the amygdala mediates most emotional reactions and that in its absence hypersexuality, hyperorality, and a release of social inhibition become evident (see Box 13-14). More recent experiments in animals, as well as the study of human patients who have bilateral damage to the amygdala (see Box 13-15, Fig. 13-11),

Box 13-14

THE LACK OF FEAR EXHIBITED BY MONKEYS WITH BILATERAL TEMPORAL LOBECTOMIES HIGHLIGHTS THE IMPORTANCE OF THE AMYGDALA TO FEAR.

In the late 1930s, Heinrich Klüver and Paul Bucy studied the effects of bilateral temporal lobectomies in monkeys. Lesioned monkeys consistently showed:

- Social disinhibition: Monkeys showed little fear and approached other monkeys readily.
- **Psychic blindness** and **hyperorality**: Monkeys treated all objects, including objects such as snakes, which normally elicit an innate fear reaction, without any signs of fear. In fact, monkeys put every object into their mouth, a consistent behavior that was interpreted as evidence that the monkeys could not recognize objects using vision. We now think that the psychic blindness noted by Klüver and Bucy was in fact **visual agnosia** or the inability to recognize and interpret visual inputs, a deficit that resulted from a lesion of visual pathways within the temporal lobe (see Chapter 16).
- **Hypersexuality**: Monkeys showed greatly increased sexual interest in each other and in their own genitalia.

The Klüver-Bucy syndrome, comprising the above set of symptoms, has profoundly influenced

our thinking about temporal lobe function generally and amygdala function more specifically. Klüver and Bucy lesioned areas of the medial temporal lobe beyond the amygdala, but the symptoms that they observed were initially ascribed to impairment of the amygdala alone. This history played a large part in the still dominant notion that the amygdala is critical to expression of fear reactions and social inhibition.

More recently, selective and bilateral lesions of the amygdala in monkeys confirm a role for the amygdala in exhibiting and recognizing fear in social circumstances. Monkeys with amygdala lesions are hypersexual and friendlier with other monkeys, approaching the other monkeys and failing to respond to other monkeys' aggression. More remarkably, lesioned monkeys are viewed as *more approachable* by normal monkeys, evidence that the amygdala plays a role in both the expression and interpretation of social threat between individuals. In sum, Klüver and Bucy's experiments have greatly colored the modern view of the amygdala, supporting a strong emphasis on fear and other negative emotions reflective of threat or danger.

CLINICAL CONDITIONS THAT RESULT IN BILATERAL DAMAGE TO THE AMYGDALA OCCUR BUT ARE RARE.

Strokes cause bilateral damage to a single structure in the brain about as often lightning hits the same spot twice, which is to say, rarely. For this reason, patients with bilateral damage to the amygdala are rare. Yet, there are two conditions that produce such damage with some frequency:

- **Limbic encephalitis** is a disease of varied etiology but usually involves a paraneoplastic (see Box 2-5) autoimmune attack on the medial temporal lobe bilaterally.
- **Urbach-Wiethe disease** is caused by a mutation in the gene for an extracellular matrix protein. Individuals with this inherited autosomal recessive disease have thickened tissues, most notably the skin and the larynx, resulting in numerous dermatological abnormalities, such as papules on the eyelids, and in hoarseness, respectively. Urbach-Wiethe disease is

heterogeneous, arising from more than 40 different mutations. In roughly half of the patients, there is bilateral calcification of the blood vessels supplying the amygdala and as a result, the amygdala is effectively lesioned (Fig. 13-11).

Studies of patients with bilateral damage to the amygdala, caused by either encephalitis or Urbach-Wiethe disease, have several reported deficits. These patients appear behaviorally disinhibited. They make inappropriately sexual innuendoes to medical personnel. When looking at a person's face, they focus on the mouth instead of the eyes, and as a consequence, cannot recognize fearful expressions. Finally, these patients have poor memory for episodes from their own life. Since the patients have normal memory for autobiographical facts, the poor episodic memory has been interpreted as a deficit in emotional memory formation.

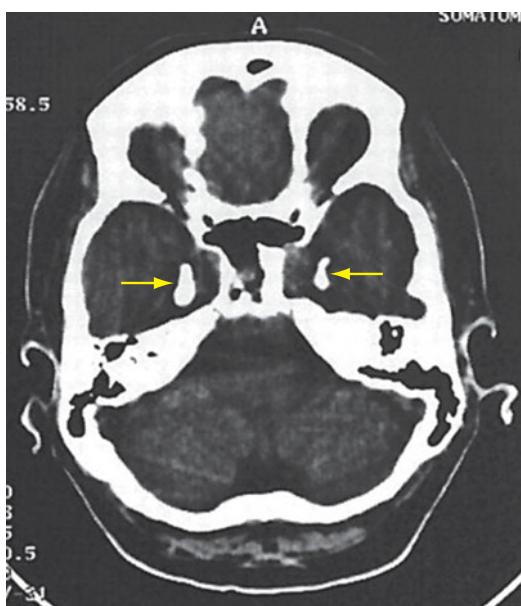


Figure 13-11. Bilateral lesions of the amygdala (yellow arrows) can be seen in this computed tomography or CT scan of a patient with Urbach-Wiethe disease.

Modified from Siebert, M., Markowitsch, H.J., and Bartel, P. Amygdala, affect and cognition: evidence from 10 patients with Urbach-Wiethe disease. *Brain* 126(12): 2627–37, 2003, with permission of the publisher, Oxford University Press.

have led to a modern, more nuanced, and still evolving, view that the amygdala serves or contributes to several functions:

- Social distance from others both during normal conditions and in reaction to threats
- Viewing, processing, and understanding the emotions in facial expressions, particularly fear
- Making emotional memories
- Evaluating the emotional valence of conditions or stimuli

The amygdala's role in assessing the fear of a situation may not be entirely one of evaluation but may also

involve how information is collected. When a patient with bilateral amygdala damage was asked to determine the emotion of a facial expression, she looked at the mouth rather than the eyes and consequently failed to detect the fearful expression (Fig. 13-12). When directly instructed to look at the eyes, the patient could correctly identify a fearful facial expression. It is interesting that the patient did not remember to look at people's eyes for long after the immediate instruction to do so and shortly lapsed back into looking only at people's mouths. This finding suggests that the amygdala may play a role in directing eye movements, and thereby the collection of visual data that would then be used to evaluate emotion.

We make emotionally laden memories far more readily than emotionally flat ones. We remember the song playing on the radio when we had an accident but not the song that played during a routine commute. Thus, the assignment of an emotional value to a situation greatly facilitates memory formation. The amygdala is critical to forming emotional memories, subconscious memories of emotions associated with stimuli. Indeed, the amygdala has been implicated in the hypervigilance and easily triggered emotional memories associated with **post-traumatic stress disorder** (see Box 13-16).

One possible synthesis of the varied roles of the amygdala would hold that the amygdala is critical to evaluating the salience and threat level, or lack thereof, of objects and conditions, functioning as something akin to the body's own Department of Homeland Security. Just as Homeland Security constantly monitors data and

updates the nation's threat level, the amygdala is likely to be important in updating the evaluation of objects and situations as they and the accompanying circumstances continually evolve.

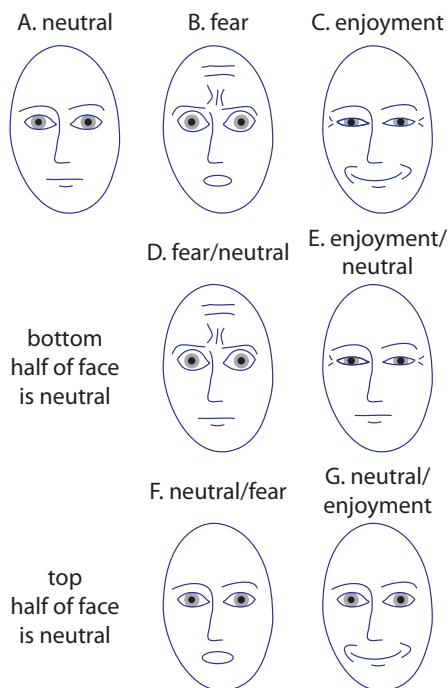


Figure 13-12. Different parts of the face are key to the communication of different emotions. A fearful facial expression (B) depends primarily on features in the upper half of the face whereas a smile of enjoyment (C) depends largely on the position of the mouth. When the upper half of a fearful expression and the lower half of a neutral face (A) are combined (D), the expression conveys fear. However, when the lower half of a fearful expression is combined with an upper face that is neutral (F), the expression does not convey fear. The converse is true for a smile of enjoyment. Combining the lower half of an expression of enjoyment with an upper face that is neutral (G) shows happy more than does the reverse (E).

THE BASAL GANGLIA CENTER AROUND THE TELENCEPHALIC STRIATUM AND PALLIDUM

Strictly speaking, the term *basal ganglia* refers to the gray matter that arises from the medial and lateral ganglionic eminences (see Chapter 3). Yet, in modern parlance, we use the term to refer to a group of nuclei linked by conceptual function rather than developmental origin. The basal

THE AMYGDALA IS HYPER- RESPONSIVE IN PEOPLE SUFFERING FROM POST- TRAUMATIC STRESS DISORDER.

Unfortunately, many of us experience trauma, whether at the hands of other humans or through natural disasters. Of those who suffer through traumatic experiences, particularly combat, rape, and disasters such as hurricanes or the 9/11 attacks on New York City, a minority develop a persistent anxiety disorder called **post-traumatic stress disorder** or **PTSD**. Post-traumatic stress disorder, colloquially referred to as **shell shock** in cases related to combat trauma, is marked by spontaneous or triggered flashbacks to the traumatic event, a flattening of affect, elevated vigilance, and a lowered startle threshold.

Post-traumatic stress disorder resembles an extreme version of fear conditioning, in which a stimulus that does not carry an affective meaning, the *conditioned stimulus*, triggers a fear reaction, the *unconditioned response*, after being paired with a negative stimulus or event, the *unconditioned stimulus*. Furthermore, whereas normally repetition of the conditioned stimulus without a subsequent unconditioned stimulus extinguishes fear conditioning, the unconditioned responses of individuals with PTSD appear impervious to extinction. To concretize this analogy, consider a soldier quietly reading in a tent. All of a sudden, the light in the tent goes out and moments later, shrapnel rips through the tent, resulting in the death of several comrades and the soldier's own severe injury. We can view the light going out as the conditioned stimulus and the shrapnel as the unconditioned stimulus. The pain and suffering of the soldier is the unconditioned response. For the individual who develops PTSD, the conditioning does not extinguish. Any version of the conditioned stimulus, even the nonthreatening occurrence of a light bulb burning out, triggers the unconditioned response. Such triggering continues to occur when the soldier returns home from the

war zone. Many believe that fear conditioning without extinction serves as a good analogy for PTSD, although all would acknowledge that PTSD also involves additional more complex processes.

The amygdala may be critical to the development of PTSD. Attention was focused on the amygdala early, given the evidence that this structure is critical to fear conditioning, the formation of emotional memories and to the experience and expression of fear. As it turns out, there are enough Vietnam veterans with both brain injuries and PTSD to allow a test of whether injury to the amygdala *protects* against the development of PTSD. Remarkably, veterans with unilateral amygdala lesions never developed PTSD whereas 40%–50% of veterans either with no brain damage or with brain damage outside of the amygdala developed PTSD. This serves as strong support for the idea that activity, perhaps hyperactivity, in the amygdala is key to establishing the PTSD state.

Not surprisingly, the amygdala is not thought to work alone in establishing PTSD. The similarities between fear conditioning and PTSD point us in the direction of prefrontal cortex as a source of extinction. An inhibitory signal from medial prefrontal cortex to amygdala is thought to be necessary for the extinction of fear conditioning. This suggests that prefrontal cortex may fail to inhibit the amygdala and thus fail to extinguish fear and panic in PTSD patients; a definitive test of this idea remains a challenge for the future. An additional challenge is to identify which individuals are susceptible to developing PTSD: Remember that only a minority of people exposed to trauma actually develop PTSD. If we could identify the individuals most vulnerable to developing PTSD, early and effective interventions may be able to prevent this potentially debilitating condition.

ganglia are critical to choosing which actions, perceptions, thoughts, and emotions will occur at any one moment (see much more in Chapter 25). At rest, the basal ganglia continually inhibit target structures and thereby act like a *big wet blanket*, suppressing all movement. When the output from the basal ganglia pauses, action—or perception or thought or emotion—is *released* from the blanket inhibition exerted by

the basal ganglia and the action, perception, thought, or emotion occurs (see Box 13-17). Information about far more candidate actions, perceptions, thoughts, or emotions enter the basal ganglia than can occur at one time. The greater input to than output from the basal ganglia reflects a greater preponderance of anatomical projections into than out of the basal ganglia. In this regard, the basal ganglia resemble another region important in modifying cerebral cortical output—the cerebellum.

The basal ganglia include the following seven structures (Fig. 13-13):

- Caudate
- Putamen
- External globus pallidus
- Internal globus pallidus
- Substantia nigra pars reticulata
- Subthalamic nucleus
- Substantia nigra pars compacta

The boxes around the **caudate** and **putamen** and around the **internal globus pallidus** and **substantia nigra pars reticulata** indicate nuclei that function together

Box 13-17

BASAL GANGLIA MOVEMENT DISORDERS CAN BE DIVIDED INTO HYPERKINETIC AND HYPOKINETIC TYPES.

Under resting conditions, the basal ganglia actively inhibit movements. Then when the drive to make a movement such as a **goal-directed movement**, a movement intended to pursue a goal such as eating, reaches sufficient urgency, the basal ganglia release that movement from inhibition. Although simplistic, this basic framework allows us to understand the two major types of basal ganglia-mediated movement disorders:

- **Hypokinetic disorders** result in a poverty of movement.
- **Hyperkinetic disorders** involve an excess of movements.

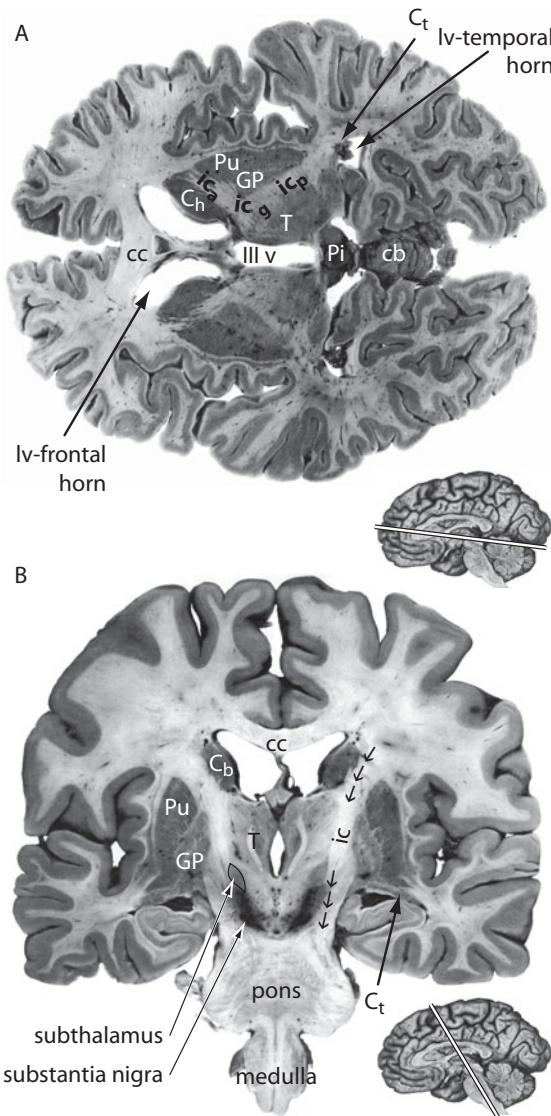
Hypokinetic disorders occur when the output from the basal ganglia continues and does not shut off and therefore does not allow movements to occur. The archetypical hypokinetic disorder is

Parkinson's disease, in which patients fail to initiate movements, **akinesia**, or move very slowly, **bradykinesia**. As explored further in Chapter 25, Parkinson's disease results from a loss of the dopaminergic projection from substantia nigra pars compacta to the striatum.

As hypokinetic disorders result from too much basal ganglia output, the reader should not be surprised that hyperkinetic disorders result from too little basal ganglia output. **Hemiballismus**, Huntington's chorea, and **dystonia** are hyperkinetic disorders that differ in pathophysiology and in the speed of the excess movements. In hemiballismus, ballistic, flailing movements occur whereas choreiform disorders like Huntington's chorea involve slower jerks and dance-like movements. Dystonia is a hyperkinetic disorder of posture in which patients adopt a fixed or slowly twisting position of their body, arm, head, or other body part.

Figure 13-13. The caudate stretches the length of the lateral ventricle (*lv*) so that the head of the caudate (*C_h* in A) abuts the lateral ventricle in the frontal lobe, the body of the caudate (*C_b* in B) abuts the lateral ventricle in the parietal lobe, and the tail of the caudate (*C_t* in A and B) abuts the lateral ventricle in the temporal lobe. No other gray matter structure abuts the lateral ventricle: *the caudate is the only gray matter area next to the lateral ventricle*, regardless of whether the section is in the horizontal (A) or coronal (B) plane. Deep to the caudate, the internal capsule (*ic*) runs, carrying fibers from the cerebral cortex to targets in the thalamus, brainstem, and spinal cord along with fibers from thalamus to cortex. The three portions of the internal capsule—the anterior limb (*ic_a* in A), genu (*ic_g* in A), and posterior limb (*ic_p* in A)—can be seen in a horizontal section. *Genu* means knee in Latin. Corticospinal fibers travel in the posterior limb of the internal capsule while corticobulbar fibers travel through the genu. Deep to the internal capsule sit the putamen (*Pu* in A and B) and the globus pallidus (*GP* in A and B). Together, the putamen and globus pallidus look like a lens, and consequently are sometimes called the *lentiform nucleus*. The other components of the basal ganglia are the subthalamicus, a lens-shaped nucleus, and the substantia nigra, both of which are visible in the section in B. Of note, in unstained sections of brain, neuromelanin contained in the neurons of substantia nigra pars compacta render the nucleus black in appearance. For orientation, the pineal gland (*Pi*), cerebellum (*cb*), corpus callosum (*cc*), thalamus (*T*), pons, medulla, and ventricles are labeled.

Photomicrographs reprinted with permission from deArmond S., et al. *Structure of the human brain: A photographic atlas*. New York: Oxford University Press, 1989.



although they are anatomically distinct. *The caudate and putamen are collectively termed the striatum and are the major input port for the basal ganglia* (Fig. 13-14). These two structures arise together during development before fibers that eventually become the internal capsule split them apart. At the rostral end of the striatum, the internal capsule is no longer present and the putamen meets the front end, or head, of the caudate. The ventral portion of this rostral striatal tissue is the **nucleus accumbens**, an important area for signaling the rewarding aspects of stimuli and often included as part of the limbic system. Neurons throughout the striatum, including those in the accumbens, use γ -aminobutyric acid (GABA) as a neurotransmitter and are inhibitory.

Like the caudate and putamen, the internal globus pallidus and substantia nigra pars reticulata arise together before being divided by fibers, in this case by axons continuing on from the internal capsule into the cerebral peduncles (Fig. 13-13). Although there is no collective term for the internal globus pallidus and substantia nigra pars reticulata, these two areas together send information out from the basal

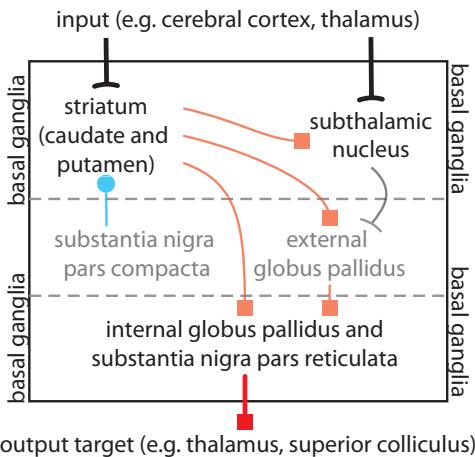


Figure 13-14. Input into the basal ganglia, the structures within the black box, comes into the striatum and subthalamic nucleus. The output of the basal ganglia arises from the internal globus pallidus and the substantia nigra pars reticulata. The inputs to the basal ganglia are glutamatergic and excitatory (black), arising primarily from cortex and thalamus. The output of the basal ganglia from the internal globus pallidus and the substantia nigra pars reticulata is GABAergic and inhibitory (red). The output of the basal ganglia targets thalamus and brainstem regions such as the superior colliculus. The external globus pallidus and subthalamic nucleus are interposed between the striatum and the output nuclei. Neurons in the striatum, both parts of the globus pallidus, and the substantia nigra pars reticulata contain GABA and are inhibitory, whereas neurons in the subthalamic nucleus contains glutamate and are excitatory. The final component of the basal ganglia, the substantia nigra pars compacta, sends dopamine-containing projections into the striatum.

Box 13-18

DOPAMINERGIC NEURONS OF THE SUBSTANTIA NIGRA CONTAIN MELANIN.

The substantia nigra, often simply called *nigra* from the Latin word for black, is dark colored in unstained tissue. The color comes from large deposits of **neuromelanin** in the compacta cells that also contain the neurotransmitter dopamine. The reason that dopaminergic neurons die in Parkinson disease patients remains unknown and an active area of investigation. It is possible that dopamine, neuromelanin, both, or neither play a role in orchestrating dopaminergic cell death in Parkinson's disease.

ganglia to either thalamic or brainstem targets. The major thalamic targets of the basal ganglia are the ventral lateral and ventral anterior thalamic nuclei, whereas a major brainstem target is the superior colliculus. Like striatal cells, neurons in the output nuclei of the basal ganglia contain GABA and are inhibitory.

The **external globus pallidus** contains GABAergic inhibitory interneurons and the **subthalamic nucleus** contains excitatory interneurons (Fig. 13-14). Both inhibitory interneurons in the external globus pallidus and excitatory interneurons in the subthalamic nucleus are interposed between the striatum and the output nuclei of the globus pallidus. The subthalamic nucleus also receives input from structures outside the basal ganglia.

Dopaminergic, or dopamine-containing, cells populate the substantia nigra pars compacta (Fig. 13-13) and

project to the striatum (Fig. 13-14). The **nigrostriatal** pathway, formed by dopaminergic nigra cells that send their axons to the striatum, provides dopamine to the striatum. This pathway is absolutely critical to movement. In the same way that a motor cannot move without oil, we cannot move to pursue our goals without striatal dopamine. Therefore, when dopaminergic nigra cells die (see Box 13-18), poverty of movement results, as exemplified by Parkinson's disease.

THE CEREBRAL CORTEX HOUSES NEURONS RESPONSIBLE FOR THE COMPLEXITY OF THE HUMAN MIND

Serving mundane and sublime functions alike, the cerebral cortex is flexible and variable enough to support the range of mammalian cognition. Due to our own human version of a cerebral cortex, we see colors, discuss what to have for dinner, make art, love passionately, aspire to explain the natural world, and build world-wide businesses. In addition, our cerebral cortex supports a multitude of cognitive functions that we share with our mammalian relatives, functions as varied as recognizing our relatives, caring for offspring, finding palatable food, voiding only at appropriate times and places, and remembering the way home.

The function of different cortical areas follows loosely from the area's distances from primary sensory and motor cortices. In other words, cortical function in the vast cortical mantle that does not contain a primary cortical area maps according to a logic that connects the functions of the primary cortical areas. An overview of cortical function from this perspective is explored below.

PRIMARY SENSORY CORTICES SUPPLY A FUNDAMENTAL PROCESSING STEP BUT NOT A COMPLETE COGNITIVE PERCEP

As you know, the occipital lobe contains the primary visual cortex necessary for processing visual information. The temporal lobe contains the primary auditory cortex necessary for hearing, and the parietal lobe houses the primary somatosensory cortex, which of course processes somatosensory information. Insular cortex contains primary gustatory cortex and receives olfactory and viscero-sensory information as well.

The two somatosensory tracts that we have followed since Chapter 9, carrying light touch, vibration and proprioception on one hand and pain and temperature information on the other, culminate in their termination in the contralateral cerebral cortex. Both somatosensory pathways synapse in the ventral posterolateral thalamus before arriving at the primary somatosensory cortex, just caudal to the central sulcus. Trigeminal pathways carrying somatosensory information from the head also ultimately reach the primary somatosensory cortex after a synapse in the ventral posteromedial thalamus. Similarly, auditory and visual information reach their respective primary cortices after synapsing in the appropriate thalamic nucleus as shown in Table 13-3.

Axons carrying sensory information leave the thalamus, join the internal capsule, and then pass through the corona radiata to reach the targeted cortical area. The axons from primary sensory cortices feeding back to thalamus travel the same route in the reverse direction, from cortex through the corona radiata and internal capsule

TABLE 13-3. THIS TABLE REVIEWS THE REPRESENTATIONS OF SENSORY STIMULI IN THE PRIMARY SENSORY CORTICES

FUNCTION	THALAMIC NUCLEUS	CORTICAL AREA TARGETED BY THALAMIC NUCLEUS
Somatosensory perception from the contralateral body	Ventral posterolateral nucleus	Primary somatosensory cortex
Somatosensory perception from the contralateral face	Ventral posteromedial nucleus	Primary somatosensory cortex
Auditory perception with <i>an emphasis</i> on input from the contralateral ear	Medial geniculate body	Primary auditory cortex
Visual perception from the contralateral visual field	Lateral geniculate body	Primary visual cortex

and then to thalamus. Primary sensory cortices carry information exclusively (somatosensory, visual) or predominantly (auditory) from the contralateral side. Note that, in the case of visual cortex, the information comes exclusively from the contralateral visual field rather than from the contralateral eye.

Primary sensory cortices are necessary bottlenecks for sensory processing bound for perception. Visual information must pass through primary visual cortex, somatosensory information through primary somatosensory cortex, and so on in order for conscious perception to occur. Yet, on their own, primary sensory cortices do not support normal perception. Rather, they process the fundamental building blocks of perception and pass this information onto other cortical areas (see Box 13-19). Furthermore, nonperceptual reactions, often termed *unconscious reactions*, to stimulation may occur through pathways that do not include primary sensory cortices. For example, people may follow with their eyes moving objects that they do not consciously perceive, a condition known as blindsight. As another example, painful stimulation of individuals with damage to the primary somatosensory cortex may result in discomfort, an affective response, even as the individual is unable to identify where or when the stimulus occurred. In other words, the response to a painful stimulus includes both affective and sensory discriminative components (see Box 13-20). The affective component gains access to the brain without a necessary stop in primary somatosensory cortex, whereas the sensory discriminative perceptual component requires an intact primary somatosensory cortex.

Box 13-19

SENSORY INFORMATION PASSES THROUGH PRIMARY SENSORY CORTICES TO REACH HIERARCHICALLY HIGHER CORTICAL AREAS CRITICAL TO NORMAL PERCEPTION.

Small lesions in primary sensory cortices typically go unnoticed. Yet, complete and bilateral lesions of the primary visual and auditory cortices cause **cortical blindness** and **deafness**, respectively. Curiously, cortical blindness is often accompanied by **anosognosia**, meaning a lack of awareness of the impairment. Patients with **Anton syndrome**, the term for cortical blindness with anosognosia, are blind. They do not blink in response to a rapidly approaching object such as the physician's hand. Yet, they vehemently *deny* that they cannot see.

Although primary sensory cortices are necessary for normal perception, they are not sufficient. The rudimentary form of sensory processing in primary sensory cortices is well exemplified by the percepts that result from activity in the primary

visual cortex arising during an epileptic seizure or a migraine aura. This activity is not a response to a stimulus but rather represents activity originating within, and restricted to, a local region. Therefore, the effects of seizure or aura-related activity tell us about the local information processing. Aberrant activity in the primary visual cortex makes people perceive flashing lights, rotating black-and-white patterns, or blind spots, termed **scotomas**. In contrast, aberrant activity in cortical areas downstream from primary visual cortex can result in reports of seeing whole landscapes or faces. The contrasting nature of these percepts reflects the rudimentary nature of sensory information in primary sensory areas, and the copious neural processing performed by downstream cortical areas.

PATIENTS WITH LESIONS OF INSULAR CORTEX HAVE ASYMBOLIA FOR PAIN.

The forebrain supports two reactions to pain. First, like other sensory inputs, painful stimulation elicits **sensory discrimination**. Using sensory discrimination we know what type of pain—burning, lancinating, stabbing, aching and so on—occurred, where, and when. Second, painful stimulation elicits an emotional reaction with motivational implications. As Sherrington put it more than a century ago, pain is “curiously imperative,” demanding an immediate and well-motivated reaction. The emotional suffering accompanying pain perception, typically termed the **affective** component of pain, feeds our motivation to react to and thereby remove ourselves from painful stimuli.

The bipartite nature of pain is accompanied by disparate cortical representations of pain. As one might expect, the primary somatosensory cortex is responsible for sensory discrimination of pain. In contrast, the affective component of pain depends on the anterior insula. Patients with anterior insular lesions can report sensory discriminative details about painful stimulation but have no or little affective reaction. In other words, these patients *do not care* about pain, a condition termed **asymbolia for pain**. The dichotomous representation of pain in two distinct regions of the brain reflects a general strategy used by the brain: divide up large and inclusive functions into component parts.

DIFFERENT VISUAL FIELD DEFICITS ARE ACCCOMPANIED BY PREDICTABLE DEFICITS IN FOREBRAIN FUNCTIONS

We followed the three long pathways responsible for somatosensation and voluntary movement through the spinal cord and brainstem because knowledge of these pathways’ anatomy allows us to deduce the location of most lesions located in the spinal cord or brainstem. Put another way, virtually all spinal and most brainstem lesions will cause a deficit in functions supported by at least one of the three long pathways introduced in Chapter 9. Upon reaching the forebrain, the diagnostic power of the three long pathways declines as all three pathways travel in the internal capsule and corona radiata to somatomotor cortex. Since great swatches of the forebrain contain no part of the three long pathways, we need an alternate strategy to deduce the location of forebrain lesions. The most useful function to test in this regard is vision because the pathway from the retina to the primary visual cortex traverses regions of forebrain not visited by the three long pathways.

Each retina receives light from an entire monocular visual field but each primary visual cortex receives input from only the contralateral hemifield (see Chapter 10 for review of basic terms). Therefore, information from each retinal nasal hemifield must cross to reach the visual cortex on the other side. The optic chiasm is where the crossing is made that provides contralateral, and only contralateral, visual field input to the cortex. Since the optic chiasm is interposed between the retina and the lateral geniculate nucleus, both visual cortex and thalamus process input from the

contralateral hemifield exclusively. Remembering a minimal amount of information will allow the reader to logically deduce the basic visual pathway:

- Information from the ipsilateral hemifield (the nasal retina) crosses at the level of the optic chiasm to reach the contralateral lateral geniculate nucleus.
- Information from the contralateral retinal hemifield (the temporal retina) bypasses the optic chiasm and heads directly for the lateral geniculate nucleus.

To understand the visual pathways, we consider the path from the eye to the contralateral visual cortex, step by step (Fig. 13-15):

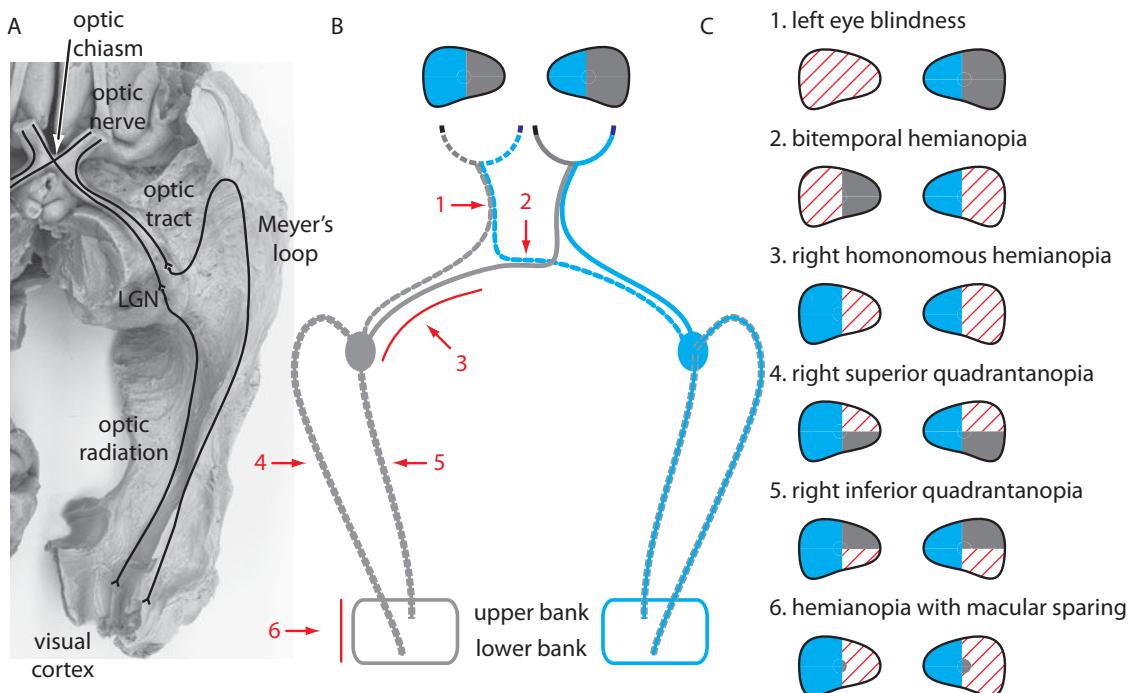


Figure 13-15. A: Visual pathways traverse the length of the telencephalon. Retinal ganglion cells carry preliminarily processed visual information from the retina to the lateral geniculate nucleus in the posterior thalamus. The axons of retinal ganglion cells travel through three structures en route to the lateral geniculate: the optic nerve, optic chiasm, and optic tract. Only axons from the nasal retina cross in the optic chiasm with temporal fibers passing laterally right into the optic tract. Thus, caudal to the chiasm, visual pathways carry homonymous visual field information. The optic tract travels laterally, past the cerebral peduncles, and ends in the lateral geniculate nucleus. After a synapse in the lateral geniculate nucleus, geniculocalcarine neurons project to primary visual cortex via the optic radiation. Axons carrying visual input from the contralateral upper quadrant of the visual field detour in front of the temporal horn of the lateral ventricle, a path known as Meyer's loop, before ending on the ventral side of the calcarine fissure. B: A schematic of the visual pathways shows the left visual field in blue and the right visual field in gray. Anterior to the chiasm, in the retina and the optic nerve, both visual hemifields are represented. Caudal to the optic chiasm, all structures carry input exclusively from the contralateral visual field. C: The effects of the most common visual pathway lesions are shown. Damage to the retina or optic nerve (1 in B) causes ipsilateral blindness. Damage to the optic chiasm (2 in B), as occurs with a large pituitary adenoma, causes a bitemporal hemianopia. Lesions anywhere along the optic tract or in the lateral geniculate nucleus (3 in B) cause a contralateral homonymous hemianopia. Damage to Meyer's loop (4 in B) causes a contralateral superior quadrantanopia, whereas damage to the optic radiation within the parietal lobe (5 in B) causes a contralateral inferior quadrantanopia. Damage to the occipital pole typically causes contralateral hemianopia with the central 5 degrees of the visual field spared. The effects of incomplete lesions at any of the locations listed above include some subset of the effects of complete lesions.

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Lesions proximal to the chiasm, meaning on the eye side of the optic chiasm, produce deficits restricted to input from the ipsilateral eye.

- *Retina:* Each retina sees light from both the ipsilateral and contralateral halves of the visual fields with the nasal retina receiving ipsilateral and the temporal retina receiving contralateral visual field input. For example, the left nasal retina receives input from the right, or contralateral, hemifield and the left temporal retina receives input from the left, or ipsilateral, hemifield. Due to the chiasmal split of input from the two hemifields, visual cortex on one side will receive inputs from the ipsilateral temporal retina and the contralateral nasal retina.
- *Optic nerve:* The situation here is no different than with the retina. Axons arising from the nasal retina carry input from the ipsilateral hemifield and axons arising from temporal retina carry input from the contralateral hemifield. As above, optic tract inputs to visual cortex will include axons from the ipsilateral temporal retina and the contralateral nasal retina, all carrying input from the contralateral hemifield.
- *Optic chiasm:* The optic chiasm sits just over the pituitary, and damage to the chiasm most often results from a pituitary adenoma (see Box 13-5). Axons arising from each nasal retina cross in the optic chiasm and join the axons arising from the contralateral temporal retina to form the optic tract.

Lesions that are retrochiasmal, meaning behind or caudal to the optic chiasm, produce homonymous, or corresponding, deficits restricted to the contralateral hemifield.

- *Optic tract:* The optic tract starts at the chiasm and ends at the lateral geniculate nucleus. En route from the chiasm to the lateral geniculate, the optic tract skirts around the cerebral peduncles, which, as you recall, carry the corticospinal and corticobulbar tracts. This means that lesions to the optic tract can produce a contralateral motor deficit as well as a contralateral hemianopia. Since the optic tract is past the crossing provided by the optic chiasm, all of its axons, whether originating from the ipsilateral or contralateral eye, carry input from the contralateral hemifield.
- *Lateral geniculate nucleus:* The situation here is no different than with the optic tract. Neurons in the lateral geniculate only respond to stimulation of the contralateral hemifield.
- *Optic radiation:* The optic radiation carries the axons of lateral geniculate neurons, which project to the primary visual cortex. As with the optic tract and lateral geniculate, the optic radiation carries inputs arising from both eyes that carry information about the contralateral

hemifield exclusively. There is one additional wrinkle in the optic radiation's pathway:

- The optic radiation splits, so that the lower part of the visual field is represented by fibers that travel along a fairly straight path from the lateral geniculate nucleus to the primary visual cortex.
- Fibers carrying input from the upper part of the visual field make a fairly large detour, passing anterior to the temporal horn of the lateral ventricle before traveling caudally to the occipital cortex, along a path known as **Meyer's loop**.
- **Primary visual cortex:** Primary visual cortex is located along the **calcarine fissure**, a deep sulcus on the medial wall of the occipital lobe (Fig. 13-16). The sulcus dorsal to the fissure represents the lower visual field, and the sulcus ventral to the fissure represents the upper visual field. Along the caudal to rostral axis of the calcarine fissure, the visual field is represented retinotopically from the center of the visual field, caudally, to the periphery of the visual field rostrally. As noted above, cortical retinotopy is marked by the disproportionate representation of the central visual field. In fact, the region representing central vision occupies more territory than is occupied by representations of all of the rest of the visual field.

In learning the visual pathways, it is important to remember, for each point along the pathway, what part of the visual field is represented, as well as the eye or eyes contributing to the pathway at that point.

The visual pathways are logical. The cortex represents the contralateral visual hemifield, while each eye receives input from the entire binocular portion of the visual field. The necessary crossing of information from the nasal retina, receiving input from the ipsilateral visual field, occurs at the optic chiasm. The only other critical piece of information to remember is that Meyer's loop contains fibers from the upper half of the contralateral hemifield.

Finally, consider how we can use visual field deficits to narrow down the location of an anatomical lesion. First, every visual field deficit can be immediately narrowed down to a lesion located before or after the chiasm based on whether the same hemifield is affected

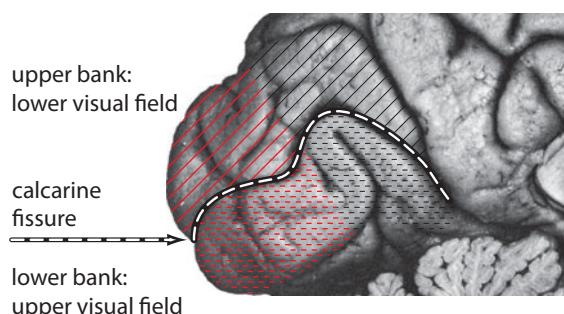


Figure 13-16. The medial surface of the occipital lobe is illustrated. Most of primary visual cortex is located along the **banks of the calcarine fissure** on the medial wall of the occipital lobe. The upper bank represents the lower visual field, whereas the upper visual field is mapped onto the lower bank. Central parts of the visual field are represented most caudally and progressively more eccentric or peripheral locations in the visual field are represented at progressively more anterior locations. The representation of the central 5 degrees of the visual field occupies more territory (red) than does the representation of the remaining portions of the visual field (black).

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LESIONS IN THE VISUAL PATHWAY LEAD TO PREDICTABLE VISUAL FIELD DEFICITS.

Because we have two eyes and a mostly binocular field of view, damage to the pathway from one eye only is often not even noticed. Even a small hole in the visual fields of both eyes is often compensated for by cortical mechanisms and therefore not noticed (see more in Chapter 16). However, careful visual field testing, mapping the visual field for each eye using small points of light, is extremely helpful in mapping the location of a lesion and can compete with modern imaging techniques in accurately locating a lesion.

Visual fields are always tested one eye at a time. The right eye's visual field is measured in a person with the left eye occluded, and the left eye's visual field in a person with the right eye occluded. Recall that features to the right of the fixation point are in the right visual field of both the left and right eyes. Thus, the right visual field includes the temporal hemifield of the right eye (containing input from the nasal retina of the right eye) and the nasal hemifield of the left eye. The suffix *-anopia*, or *-anopsia*, is used to denote a loss of sight. With this terminology, we are now ready to name some of the common visual field deficits, all of which are illustrated in Figure 13-17.

A lesion at the midline of the optic chiasm, most frequently the result of a pituitary tumor, will cause a bitemporal hemianopia, which means that the patient cannot see the temporal hemifield of either eye. Since visual pathways beyond the chiasm carry only contralateral field information, retrochiasmal lesions produce homonymous, or consistent, visual field deficits in both eyes. For example, a complete lesion of the optic tract or lateral geniculate nucleus results in a contralateral **homonymous hemianopia**, meaning that the affected individual will be blind to the contralateral visual field. For example, a lesion of the left optic tract will impair vision of the right hemifield in both the right and left eyes.

Upon exiting the lateral geniculate nucleus, the optic radiation splits into two parts so that information from the upper and lower contralateral quadrants of the visual field travel separately. Lesions in the optic radiation typically knock out only one part of the radiation and consequently, only a quarter of the visual field at most. For example, lesions

that impinge on Meyer's loop impair vision of the upper half of the contralateral hemifield in both eyes, a condition termed **homonymous superior quadrantanopia**. Lesions at the back of the head, either due to blunt trauma or to ischemia in the territory of the posterior cerebral artery (see Chapter 14), can cause complete blindness if they are bilateral or a hemianopia if restricted to one side. Yet, in many such cases, central vision or some portion of it is spared. The reason for such **macular sparing** is unclear but may have to do with redundancies in the representation of central vision within visual cortex.

As mentioned in Chapter 10, very few lay people are familiar with either the term or the concept of visual fields. Therefore, a person's complaint of a problem with vision in one eye should simply serve as the impetus for visual field testing. The individual may be correct or may have misinterpreted a problem with a hemifield as a problem with the eye on that side.

Detailed visual field assessments are available using a computerized test of a patient's ability to detect spots of light randomly distributed throughout the visual field of each eye. Yet, a crude version of visual field testing can be done by simply asking a patient to fixate straight ahead and report when they detect the appearance of an object such as the point of a pencil as the tester brings that object in from the periphery of each quadrant (nasal, nasal-superior, superior, temporal-superior, and so on). If all is well, the patient reports detecting peripheral objects throughout the visual field. If not, you have a crude estimate of the margins of the patient's visual impairment. Finally, in patients with compromised communication skills, such as an individual with Wernicke's aphasia, testing whether a patient blinks to "threat," a rapid movement of your hand toward the patient's face, can crudely map out the margins of a visual impairment. Normally, a person blinks if he or she can see the approach of the hand. However, an individual with, for example, bitemporal hemianopia will not blink when an object approaches rapidly from the temporal edge but will blink to a threat approaching from straight ahead.

in both eyes (see Box 13-21). Second, the divergence of the optic radiation into tracts carrying input from the upper and lower quarter fields means that a lesion of the optic radiation will produce a deficit restricted to one or the other contralateral quarter field. In contrast, a lesion in the optic tract or lateral geniculate typically produces a deficit that includes parts of both upper and lower quarter fields. Finally, since the visual pathway wends its way from the front to the back of the brain, a lesion caused by a stroke or a tumor will rarely affect visual pathways in isolation. Instead, accompanying symptoms, such as contralateral paralysis or a hormonal disturbance, greatly aid us in localizing lesions that cause visual field deficits.

VISUAL INPUT IS TRANSFORMED INTO INFORMATION NEEDED TO GUIDE MOVEMENT AND INFORM PERCEPTION

The occipital pole houses primary visual cortex. Cortical regions downstream from primary visual cortex provide a more and more complex synthesis of the visual world, integrating visual building blocks—spots, edges, and the like—into complete scenes and recognizable objects. Two streams or pathways employed for different purposes emanate from visual cortex. The **dorsal visual stream** bound for the parietal cortex concerns the location and speed of visual objects (Fig. 13-17). This stream is used to identify the location of moving objects, visually guide movements, and to understand the observed movements of others'. Ultimately information carried in the dorsal visual stream is sent toward motor and premotor areas, where it is invaluable to adjusting movements based on sensory input. Without such information, we might throw off target, break an egg by holding it with too much force, or injure ourselves by grabbing a thistle.

The **ventral visual stream** bound for the temporal cortex concerns the appearance of visual objects and is used to identify what we are seeing, so that we can understand the meaning of the visual world (Fig. 13-17). Somatosensory and auditory information joins with visual information in the inferotemporal lobe, where recognition and attachment of meaning to objects occurs (see Box 13-22).

THE SENSORIMOTOR CORTEX IS CRITICAL TO VOLITIONAL ACTIONS

The primary motor cortex and neighboring regions, most notably the primary somatosensory cortex and regions anterior to primary motor cortex, give rise to the corticobulbar and corticospinal tracts. Instructions for voluntary

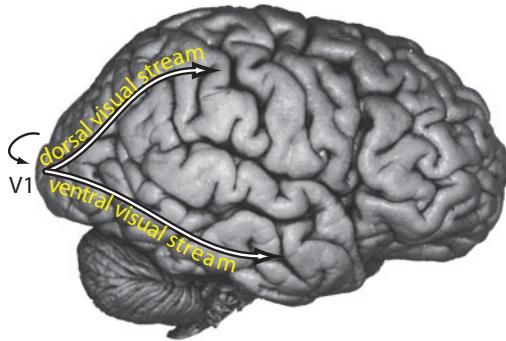


Figure 13-17. From primary visual cortex (V1), information flows in two principal directions. The dorsal visual stream, carrying information about the location and movement of visual objects heads toward parietal cortex. The ventral visual stream, carrying information about the form, appearance, and ultimately meaning of visual objects heads toward the lateral part of the inferior temporal lobe.

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ventral lateral thalamus—allow the cerebellum and basal ganglia to modulate the final motor command arising from cortex and traveling in the corticospinal and corticobulbar tracts. Axons of the corticospinal and corticobulbar tracts course through the corona radiata before becoming part of the internal capsule. As the reader recalls, corticospinal tract axons then travel through the cerebral peduncles, the basis pontis, and the medullary pyramids before entering either the ventral or dorsolateral funiculus of the spinal cord.

Box 13-22

THE TARGET OF THE VENTRAL VISUAL STREAM IS CRITICAL TO IMBUING PERCEPTIONS WITH MEANING.

The ventral visual stream carries visual information to the inferior temporal lobe where that information is used to not only build percepts of observed objects but also to connect those percepts to their meaning. The inability to connect a percept to its meaning, even when there is no impairment in sensory perception, is termed *agnosia*. There are many types of agnosia. For instance, the inability to recognize faces is termed **prosopagnosia** (see Chapter 16). An example of *form* agnosia, the inability to recognize a whole form despite accurately perceiving the

actions reach motoneurons in the brainstem and spinal cord only by way of the descending tracts. Therefore, the sources of descending motor tracts from cortex, collectively termed the **sensormotor cortex** (Fig. 13-18), form a bottleneck for voluntary movement. The impetus to act and the plan for a movement may arise elsewhere, but the most basic building blocks, the component movements, necessary for fully realized *voluntary actions* pass through primary motor cortex to the corticobulbar and corticospinal tracts (see Box 13-23).

Reciprocal connections between motor cortex and the “motor” nuclei of the thalamus—ventral anterior and

form’s components was described in Chapter 1. As the example of Dr. P. illustrates, seeing a green tube with red oblong petals does not a rose make. Since somatosensory, auditory, and olfactory as well as visual information reach the inferior temporal lobe, individuals with lesions that disconnect one sensory modality from the inferior temporal lobe may use a different sensory modality to identify an object. This was the case for Dr. P., who readily identified a rose by smell although he was unable to do so by sight.

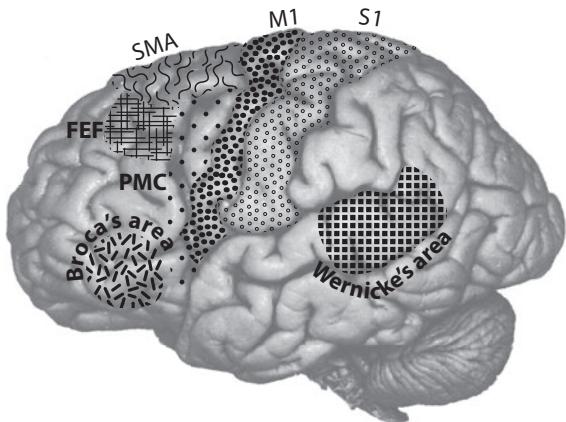


Figure 13-18. The sensorimotor cortex includes primary motor cortex (*M₁*), supplementary motor area (SMA), premotor cortex (PMC), and primary somatosensory cortex (*S₁*), all of which contribute to the corticobulbar and corticospinal tracts. Supplementary motor area and premotor cortex are located just rostral to primary motor cortex and are needed to plan any but the simplest one-muscle, one-joint movement. The primary somatosensory cortex receives somatosensory and vestibular information that provides critical information about where our body is, the state of our muscles and joints, the force needed to carry loads of different weights, and the consistency and texture of the objects that we manipulate. Broca's area and the frontal eye fields (FEF) are cortical areas needed for specialized movements: speech and eye movements, respectively. Wernicke's area is located in the superior temporal gyrus of the dominant hemisphere and is responsible for understanding spoken language. Broca's area is located in the inferior frontal gyrus, anterior to representations of the tongue and larynx in primary motor cortex. Broca's area, present in the dominant hemisphere, is responsible for producing spoken language. The arcuate fasciculus (not shown) connects Wernicke's area to Broca's area.

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FRONTAL CORTEX TRANSFORMS MOTIVATION INTO A STRATEGY FOR ACTION AND THEN INTO COMMANDS FOR MOVEMENT

Anterior to the primary motor cortex are the **premotor cortex** and **supplementary motor area**, regions critical to movement planning. These areas chain together simple movements into more complex ones. For example, as we learn to play a new tune on the piano or how to flip an omelet, or even as we simply mentally rehearse these movements, we use our supplementary motor area. Two regions specialized for particular types of movements are found in the frontal cortex rostral to the primary motor cortex and premotor cortex. **Broca's area** is necessary for speech production (see below), and the **frontal eye fields** (see Chapter 26) are necessary for voluntary eye movements (Fig. 13-18). Collectively, primary motor cortex, premotor cortex, supplementary motor area, Broca's area, and the frontal eye fields constitute somatomotor cortex.

The insula and limbic regions of frontal cortex are critical to the appreciation of tastes and odors and to the processing of the internal physiological state, inputs that have a particularly direct influence on our emotions and drive to act. A bad odor compels us to get away, just as a tasty odor motivates us to seek out its source and sickness drains us of the motivation to do anything. From this perspective, we can view the frontal cortex as being bracketed by regions critical to

Box 13-23

SIMPLE TWITCHES RESULT FROM PRIMARY MOTOR CORTEX ACTIVITY.

The brain itself is insensate, meaning that cutting, prodding, or damaging the brain does not give rise to somatic sensations. **Wilder Penfield**, a famous neurosurgeon at the Montreal Neurological Institute, took great advantage of this fact by operating on awake patients. He electrically stimulated sites all over the convexity of the brains and recorded the resulting movements and oral reports of perceptions and feelings. In this way, Penfield produced a functional map of the human brain. Today, neurosurgeons still operate on awake patients and use

neurophysiological techniques to map the locations of both critical functions, such as speech, and damaged regions. To return to the subject at hand, stimulation in the primary motor cortex produces contralateral muscle contractions in the body part corresponding to the area of the motor homunculus stimulated. The idea that primary motor cortex activity produces simple movements is further corroborated by the muscle contractions that result from seizure activity in the primary motor cortex.

Box 13-24

WORKING MEMORY IS A FORM OF MEMORY THAT IS AVAILABLE ONLY TRANSIENTLY.

Working memory is a form of short-term memory that is available at any one moment in time. Working memory exists prior to the consolidation of a lasting memory. For example, when we are told a telephone number, we repeat it over and over until we can write it down or dial it. The repetition of the number is an example of working memory. The contents of working memory may make it into long-term memory or may be forgotten.

motivation and regions critical to movement. The intervening parts of frontal cortex are termed the **prefrontal cortex**. Prefrontal cortex organizes behavior by using **working memory** (see Box 13-24) to translate personal and social motivations into a plan for movement. In essence, prefrontal cortex addresses the questions “Why move? Why do anything?” and answers either query by initiating an action or refraining from action (see Box 13-25). Therefore, prefrontal cortex organizes and prioritizes behavior to connect motivational areas to motor areas of cortex. In the absence of prefrontal function, little or no behavior is initiated.

Taken as a whole, the prefrontal cortex is the center for multitasking, effectively responding to unexpected events while engaged in a task. For example, how should one respond when the phone rings, the baby cries, and a burning smell begins to waft in from the kitchen while sitting at a desk studying for an exam? The motivation to either keep studying or respond to one or more of the salient events is worked out in the most anterior portions of the prefrontal cortex. One strategy of response might be to check for a possible fire, put it out if necessary, and then go get the baby while ignoring the phone. An alternate strategy might be to pick up the baby and run out while ignoring the phone and accepting that the apartment may burn down. Once fiery disaster is averted and the baby calmed, the anterior prefrontal cortex dictates whether one returns to the original, still unfinished task of studying or goes drinking to recover from the ordeal. The strategies considered and the one adopted by an individual speak to that person's temperament and life experiences and are fundamental expressions of that person's self. Thus, the heroic person considers only behaviors that result in saving the baby, while the obedient person may consider first answering the phone.

The ability, or lack thereof, to play well with others, the capacity to stay on task or to divert one's attention, and myriad other high-level choices are worked out by anterior regions of prefrontal cortex. Progressively more caudal portions of

PREFRONTAL FUNCTIONS ARE SEVERELY IMPAIRED IN LOBOTOMIZED INDIVIDUALS.

For several decades, neuroscientists have told the story of **Phineas Gage** in order to illustrate the function of the prefrontal cortex. Phineas Gage was a 19th-century railroad building foreman who suffered a penetrating head wound and was said to never be the same. In the oft-told story, Gage was “no longer Gage” after the accident. Although popular prior to the accident, Gage became socially inappropriate and behaviorally disinhibited. Recent evidence raises strong doubts about the accuracy of the Gage story as commonly told. Specifically, the exact areas damaged and changes in Gage’s behavior from before the accident to after his initial recovery are unclear, suggesting that the Gage story is at least partially apocryphal and should no longer sway our thinking about prefrontal function in humans.

The story of countless individuals who underwent a **frontal lobotomy**, the first widely used form of **psychosurgery**, paints a dramatic although murky picture of prefrontal function. **Egas Moniz**, a Portuguese neurologist, invented a surgical procedure that he called frontal **leucotomy** in 1935. Moniz was motivated by the desire to cure patients with mental illnesses such as depression, schizophrenia, and panic disorder, patients for whom only drastic treatments such as **insulin shock therapy** were available at the time. Moniz designed the leucotome, an instrument with a loop at the end, to sever the connections between the frontal lobes and the thalamus in an effort to deprive diseased parts of the brain an avenue of expression. He reported that most patients benefited and none were harmed by frontal leucotomy. After Moniz’s pioneering work, many physicians began performing leucotomies, or variations thereupon, around the world. It is interesting to note that Moniz also invented **cerebral angiography**, a method for visualizing cerebral blood vessels in standard use today, in the late 1920s. Yet, Moniz was awarded the 1949 Nobel Prize for Physiology and Medicine for the leucotomy, which has fallen into disrepute (see below), and not for cerebral angiography.

The most active psychosurgeon in America was Walter Freeman, a neurologist, who followed Moniz’s work and performed frontal **lobotomies**,

as he called them, in America from 1936 until 1967. In order to make the lobotomy accessible to the myriads of individuals he felt could benefit from it, Freeman simplified the procedure. Freeman lobotomized thousands by entering the brain through the eye with a leucotome, or icepick, and then twirling the leucotome around to cut the intervening brain tissue. Freeman performed this simple transorbital lobotomy in his office or in makeshift surgical arenas around the country. Freeman took an evangelical view of the lobotomy, earning him infamy in the history of medical science. The fascinating story of Freeman and of psychosurgery more generally are detailed in *The Lobotomist* by Jack El-Hai and in *Great and Desperate Cures: The Rise and Decline of Psychosurgery and Other Radical Treatments for Mental Illness* by Elliot S. Valenstein. A heart-wrenching account of a man who underwent a transorbital lobotomy in Freeman’s office at the age of 12 is given in *My Lobotomy* by Howard Dully and Charles Fleming (Three Rivers Press, New York, 2007).

The development of psychotropic drugs, notably the antipsychotic **Thorazine**, initiated the decline of the lobotomy. When first introduced, Thorazine was viewed as a chemical lobotomy. Currently, psychosurgery has made something of a comeback but with important differences from the lobotomies performed by Freeman and others. First, the procedures are given to desperately ill patients and informed consent is rigorously required. Second, the procedures are targeted at lesioning or stimulating specific parts of the brain, such as the cingulate gyrus or subthalamic nucleus.

Moving beyond the history, what effect did lobotomies have on behavior? The general consensus is that destruction of frontal lobe white matter made individuals more docile and easier to manage. Yet, the operations widely varied, as is to be expected from the transorbital operation—the twirling of an ice pick is hard to standardize. Consequently, the effects of lobotomies widely varied. The stereotypical picture of lobotomized people is of individuals who seldom initiate behavior or conversation, an image that fits well with our conception that the frontal lobes are critical to turning motivation into planning and planning into action.

frontal cortex then transform choices and strategy into an actual sequence of movements. Whereas damage to any part of motor cortex impairs some aspect of movement per se, individuals with damage to the prefrontal cortex often have problems in supervising or sequencing behavior, particularly when interruptions to the task at hand occur, and therefore benefit from highly structured and consistent expectations, as well as a predictable environment.

LANGUAGE AND HANDEDNESS HEAD THE LIST OF LATERALIZED FUNCTIONS

Throughout most of the spinal cord, brainstem, and forebrain, structures on the left and right side of the brain perform the same function for different body parts or regions of space. The left ventrolateral quadrant of the spinal cord carries pain and temperature information from the right body, and the right ventrolateral quadrant carries pain and temperature information from the left; left visual cortex codes for the right visual field, and right visual cortex for left visual field and so on. However, there are notable exceptions to this rule. One exception is that we, or at least the vast majority of us, have a dominant hand, a hand that we prefer to use over the other.

In most people, left- and right-handed alike, the left cerebral hemisphere is **dominant**, meaning that it is responsible for language. Understanding and producing speech primarily depends on **Wernicke's** and Broca's areas, respectively, *in the dominant hemisphere* (Fig. 13-18). Damage to either language area, or to the **arcuate fasciculus** which joins them, impairs spoken communication, causing some type of **aphasia**, or difficulty in communication using spoken language (see Box 13-26). Aphasia is always accompanied by at least some deficit in writing, **agraphia**, and may, or may not, be accompanied by additional deficits in reading, **alexia**, or singing, **amusia**.

Damage to the nondominant hemisphere can also impact language. Notably, problems with understanding and producing **prosody**, the communicative tone that accompanies speech, are caused by lesions in the nondominant hemisphere (see Chapter 17). A person who speaks without prosody sounds monotonic, and a person deaf to the prosody of speech has great difficulty understanding a speaker's intended meaning and emphasis.

THE HIPPOCAMPUS TURNS EXPERIENCES INTO MEMORIES AND THEN SENDS THE MEMORIES OUT FOR LONG-TERM STORAGE

In 1953, a young man named Henry Gustav Molaison, known as patient **HM** (see Box 13-27) until his death in 2008, sought neurosurgical treatment for debilitating epileptic seizures. **Epileptic foci** (see Box 13-28) for HM's seizures

DOMINANT HEMISPHERIC LESIONS CAN CAUSE A DISORDER OF LANGUAGE.

An impairment of language is termed **aphasia**. The type of aphasia depends on the location of the lesion. Broadly speaking, there are three types of aphasia:

- Wernicke's aphasia, also known as **fluent aphasia** or **receptive aphasia** results from a lesion in Wernicke's area. Patients have difficulty understanding spoken language. Yet, their speech remains relatively fluent at least in terms of articulation, presumably because Broca's area is intact. Wernicke's aphasia is a difficult problem to treat as communication with the affected patient is limited.
- **Broca's aphasia**, also known as **nonfluent aphasia** or **motor aphasia**, is caused by damage to Broca's area, which sits anterior to the tongue and larynx representations in primary motor cortex of the dominant hemisphere. Patients have difficulty producing fluent spoken language but can understand spoken language

relatively well, presumably because Wernicke's area is intact.

- **Conduction aphasia**, a rarer form of aphasia than the other two, results from damage to the **arcuate fasciculus** that connects Wernicke's and Broca's areas. The cardinal sign of a conduction aphasia is difficulty in repeating spoken language, presumably due to the disconnection between where speech is understood, Wernicke's area, and where speech is produced, Broca's area.

Understanding speech and producing speech are related tasks. Patients with Broca's aphasia have some impairment in understanding spoken language. Patients with Wernicke's aphasia can neither understand nor produce meaningful speech. Thus, evidence suggests that speech production aids in speech comprehension and that speech comprehension is critical to meaningful speech production.

HM WAS REVEALED TO BE HENRY GUSTAV MOLAISON UPON HIS DEATH IN 2008.

It is customary to refer to patients, dead or alive, by their initials. As long as he was alive, Molaison was always referred to as **HM**. The posthumous release of Molaison's name to the public was done with the permission of Molaison's legal guardian. In keeping with the custom and the large extant literature on "HM," we will refer to Molaison as HM henceforth.

were present bilaterally in each temporal lobe. Consequently, William Scoville, a Connecticut neurosurgeon, removed both of HM's medial temporal lobes. The surgery had the intended effect of completely resolving HM's epilepsy: he never had another seizure. Unfortunately, the surgery also had an unintended consequence as HM, 27 years old at the time of the surgery, became profoundly **amnesic** and never made another new declarative memory (see Box 13-29) over the next 55 years of his life.

Once Scoville realized that HM had a severe impairment of memory, he took HM to the Montreal Neurologic Institute, with the result that a neuropsychologist named **Brenda Milner** met HM. Milner, and eventually several of her students, studied and performed rigorous psychological testing on HM over the course of six decades. Milner's tests confirmed that HM had severe amnesia. Scoville and Milner published this fundamental result in 1957, and consequently, no other patient has had the medial temporal lobes removed bilaterally. Additionally, Milner's and others' studies of HM and other patients with medial temporal lobe damage (see Box 13-30) opened the door to our modern neurobiological view of memory, which includes the following essential ideas:

- The hippocampus is required for the formation of new, long-term declarative memories (see Box 13-31).

EPILEPTIC FOCI ARE REGIONS OF DAMAGED BRAIN TISSUE WHERE SEIZURE ACTIVITY STARTS.

Epileptic foci are areas of the brain, typically in the cerebral cortex, where seizure activity begins. With time and with each seizure that begins at a focus, the threshold to elicit a seizure decreases, rendering the region more and more epileptogenic. In some cases, a traumatic injury to the brain resulting in frank damage to the cortex causes a focus but in many cases, the root cause is unclear. When pharmacological treatment fails to prevent seizures and when the seizures become debilitating, the next step is the neurosurgical removal of the epileptic focus or foci.

- Several forms of memory, including working, motor, procedural, and implicit memory, do not depend on the hippocampus. For example, HM learned to trace figures viewed through a mirror at a rate that did not differ from that of individuals without declarative memory problems.
- The long-term storage of declarative memories does not depend on the hippocampus. The import of this is that individuals with hippocampal damage, including HM, retain old memories made prior to the hippocampal damage. For example, in the early 1980s, HM was asked who was president, as part of a standard mental status exam. He was uncertain. When told that it was Ronald Reagan, HM responded with surprise and an embarrassed laugh saying, politely, “Well, he was a good actor.” At each subsequent exam over several months, he responded in exactly the same manner. The examiner in each case had never heard HM laugh before.

Even without the ability to make new memories, HM remained the same affable person that he was before his operation. His good-natured personality shone through his disability, and consequently, he was loved by those that worked with him. Although he was not survived by any family, HM left behind devoted friends among the scientists who tested him over the course of six decades, as well as myriads of grateful admirers who feel a deep indebtedness for all that he taught us.

The amnesia that results from bilateral hippocampal damage, as well as from a number of other conditions such as Alzheimer disease, differs from what many call “Hollywood amnesia,” the version of amnesia seen in most movies. Alfred Hitchcock’s *Spellbound* is a classic example of Hollywood amnesia. The character played by Gregory Peck has no idea of who he is and cannot recall any past events, but makes new memories completely normally. In stark contrast, most amnesia is **anterograde**, meaning that new memories cannot be formed. Anterograde amnesia is often accompanied by **graded retrograde** amnesia, meaning a failure to remember past events that is most severe for the immediate past and least severe for the long ago past. Retrograde amnesia rarely occurs unaccompanied by at least some period of anterograde amnesia, whereas states of anterograde amnesia are often accompanied by graded retrograde amnesia. For example, a person with graded retrograde amnesia may fail to remember the minutes or hours prior to a car accident while retaining normal recall of life prior to the accident. The same person also shows anterograde amnesia in failing to remember the immediate aftermath of the accident.

Once a long-term memory is formed, that memory is not written in stone. Recent evidence suggests that memories are retrieved and then reconsolidated by the hippocampus. The idea is that after each retrieval of a long-term memory, that memory is reformed or reconsolidated by the hippocampus before once again being shipped out to another area of cortex. This idea, while still controversial, allows us to understand several features of memory. First, memories degrade over time. Recall of an evening out is filled with far more details on the following day than when remembered a year later. Second, memory is facilitated by frequent recall and therefore frequent reconsolidation. A story that is told daily is more easily recalled than a story told once or infrequently. Third, memories can change. For example, eyewitnesses often recall one set of events immediately after a crime

Box 13-29

DECLARATIVE MEMORY IS THE EXPLICIT MEMORY OF FACTS.

Declarative or explicit memory has two components: **semantic** and **episodic**. Semantic memory is essentially vocabulary: knowing the word for an apple or a flash drive and the name of your teacher or friend and the name of a street and so on. Recalling the facts of events experienced utilizes episodic memory. So, for instance, in recollecting the trip to pick up a new puppy, the mode of transportation, the destination, the identities of the travelers are all episodic memories. On the other hand, the smile on your face every time you pass the place where you picked up your now beloved dog, is an implicit, emotional memory.

Testing for declarative memory is simple. First, you ask the person to remember a few words or numbers. To ensure that they heard the list, the person should immediately repeat the items back to you. After a short interval, 5 minutes or so, you will ask the person to recall the list. During the interval, the person must be distracted and focused

on another task to prevent continuous rehearsal of the list using working memory. Finally, when the interval is over, ask the person to recall the words or numbers that you asked them to remember. People with normal memories have total recall whereas an individual like HM with **dense**, meaning severe, amnesia will not know what you are talking about. They will not even remember that you asked them to remember anything.

The analog to declarative memory in nonhuman mammals is an interesting and still open question. In rats, many hippocampal neurons preferentially fire when the animal is at a certain position in the environment. Consequently, neurons with a preference for certain locations are called **place cells**. As the integration of information from place cells could render a map of the environment, spatial location may be the natural object of declarative memory in mammals without language.

Box 13-30

THE HIPPOCAMPUS IS PARTICULARLY SENSITIVE TO LOW LEVELS OF OXYGEN.

The reader may wonder how many patients with bilateral medial temporal lobe damage occur “naturally.” Unfortunately, a fair number of individuals suffer bilateral hippocampal damage as a result of **hypoxia**, or low levels of oxygen. Hypoxia may occur for a number of reasons, including cardiac arrest. As it turns out, the brain region most sensitive to hypoxic damage is the hippocampus. Therefore, the hippocampi of individuals who lack sufficient oxygen for a stretch of time, regardless of the cause, are often damaged bilaterally.

and a slightly different set of events years later. Finally, we can use reconsolidation to understand graded retrograde amnesia. We consider two memories, of equally strong emotional impact—one formed by HM at age 15, 12 years before his operation, and one formed by HM in the month before his operation. In the former case, HM presumably retrieved and consolidated the memory thousands of times. In contrast, in the case of a memory formed just a month before losing all hippocampal function, HM would have had time to retrieve the memory far fewer times. This perspective suggests that older memories are stronger and persist longer than more recently formed memories, as is indeed the case. In sum, reconsolidation may underlie the common finding that retrograde amnesia is graded, so that memories are lost in the reverse chronological order from which they are formed.

THE PARAHIPPOCAMPAL GYRUS AND FORNIX PROVIDE PORTALS INTO AND OUT OF THE HIPPOCAMPUS

Since we form memories of all types of events, it should not be surprising that the hippocampus receives input from regions throughout the cortical mantle. Most of this input funnels into the hippocampus via the neighboring

SUBSEQUENTLY IDENTIFIED AMNESIC PATIENTS HAVE GREATLY AUGMENTED WHAT WE LEARNED FROM HM.

Scoville took out large portions of HM's medial temporal lobe, including not only the hippocampus but also the parahippocampal gyrus and the amygdala, and the consequence was a particularly dense amnesia. Since the lesions were so large and included several structures, it was not immediately clear which medial temporal lobe structure or structures were critical to declarative memory. Following Scoville and Milner's report on HM, additional patients with more selective lesions were identified and tested. The upshot of all of this research is that bilateral damage restricted to the hippocampus produces amnesia.

entorhinal cortex. Most of the output from the hippocampus also exits via a hippocampal neighbor, the **subiculum**. The subiculum, entorhinal cortex, and hippocampus are all housed within the **parahippocampal gyrus** (Figs. 13-1, 13-3). Since most of the input to and output from the hippocampus courses through the parahippocampal gyrus, lesions there produce an amnesia very similar to that produced by lesions of the hippocampus proper.

The fornix is a prominent forebrain tract that serves hippocampal connections, both into and out of forebrain areas more distant than the parahippocampal gyrus (Fig. 13-5). Axons leaving the hippocampus curve around the lateral ventricle as part of the fornix to end in the anterior thalamus and in the mammillary bodies. Medial diencephalic lesions, particularly those of the mammillary bodies, impair declarative memory (see Box 12-16).

CORTICAL ANATOMY IS THE SUBSTRATE FOR INTELLECTUAL ABILITY

In the past, psychologists have defined ***g*** as a factor that quantifies a measure of general intelligence. Under this construct, an individual's ability at each type of cognitive task is the product of *g* and a factor related to specific cognitive abilities. The concept of *g* has not been widely accepted in neuroscience. In contrast to the prediction that all types of intellectual aptitude are correlated, it is clear that normal individuals can have widely disparate abilities. Moreover, individuals with **intellectual disability**, a heterogeneous group of conditions previously termed **mental retardation**, have gross deficits in some cognitive functions and no measurable differences from normal individuals in other cognitive functions (see Box 13-32). In fact, individuals with **savant syndrome** are characterized by an **exceptional** aptitude in one area—such as musical ability, visual memory, or calculations—and below-normal intellectual abilities in the remaining areas.

One popular idea has been that within a species, brain size is related to an individual's intelligence. This idea is supported by the prevalence of small, termed **microencephalic**, and **lissencephalic**, or brains with minimal gyration, brains among intellectually disabled individuals. Yet, **macrocephaly**, or a significantly larger than normal brain, can accompany either normal intelligence or intellectual impairment as occurs in many conditions including **autism** and **fragile X syndrome**.

An evolving view holds that **intelligences** are emergent properties of the cerebral cortex. Different cortical areas support different cognitive abilities. Widespread anatomical changes, such as those found in individuals with **Down syndrome**, are likely to impair numerous cognitive functions. Moreover, cortical function may be delicately tuned, so that numerous types of changes—fewer neurons, more neurons, misdirected dendrites, extra synapses, loss of a signaling molecule, and so on—may all lead to cortical circuit dysfunction and therefore

INTELLECTUAL DISABILITY AFFECTS 1%–3% OF THE POPULATION.

Intellectual disability, previously termed **mental retardation**, is a type of **developmental disability** in which children have a low intelligence quotient or IQ and show impairment in additional cognitive functions. Intellectually disabled individuals typically fail to develop normal skills such as language, washing and dressing themselves, and socializing with others. Hundreds of causes result in intellectual disability with the most common genetic defects being **Down syndrome**, **phenylketonuria** or **PKU**, and **fragile X syndrome**. Nongenetic causes of intellectual disability include maternal alcoholism, which gives rise to **fetal alcohol syndrome**, certain maternal or neonatal infections, hypoxia during delivery and severe malnutrition. The latter is, tragically, a leading cause of intellectual disability in developing countries.

Regardless of the cause, the anatomical substrate for below-average intellectual development appears to be distributed differentially across the cerebral, and in many cases cerebellar, cortex. In the case of Down syndrome, both the cerebral and cerebellar cortices are smaller, with fewer neurons and synapses than in individuals of normal intelligence.

Cortical regions involved in language, motor control, and working memory are particularly impaired as are the functions themselves. No treatment exists that either slows or reverses the deteriorating course of intellectual disability in most patients, including those with Down syndrome. In such cases, education, behavioral therapy, and management are employed to reduce stressors and optimize predictability in the patient's environment.

There is one notable exception to the lack of available treatments for patients with an intellectual disability-causing disease. If individuals with phenylketonuria adhere to a diet that lacks phenylalanine starting immediately after birth, a harmful buildup of phenylalanine can be avoided and normal intellectual development can occur. To enable the prompt identification of babies with PKU, typically caused by a mutation in the phenylalanine hydroxylase gene (see Box 7-8), all babies born in hospitals in industrialized countries are tested for PKU at birth. For the phenylalanine-free or “PKU diet” to be effective, it must be a life-long diet and must be followed with particular care during the developmental years.

cognitive impairment. When these changes are restricted, the result may be tone deafness or poor language skills, and when the changes are widespread, the condition that we term intellectual disability may be the result.



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CHAPTER 14

FOLLOWING THE NUTRIENTS: BLOOD SUPPLY, BLOOD–BRAIN BARRIER, AND VENTRICLES

Like all other tissues, the brain requires oxygen and nutrients to function and waste disposal to prevent potentially toxic consequences. Yet, the brain differs from most body tissues in important ways. First, the neural tissue has a far higher oxygen requirement than any other tissue. Second, the central nervous system (CNS) does not receive oxygen and nutrients directly from capillary blood. Instead, the brain and spinal cord are bathed in cerebrospinal fluid, or CSF, which is essentially a watery, filtered version of blood. Third, the brain is contained within an unyielding bony cavity, the cranium. As we shall see, the cranium complicates the otherwise simple pressure relationship between arterial and venous blood flow. In this chapter, we follow oxygen and nutrients from arrival to disposal by focusing on:

- The arterial blood supply to the brain and spinal cord
- The blood–brain barrier
- The collection and drainage of venous blood from the brain

As nutrients travel from arterial blood to brain, and waste products from brain to venous blood, the paths critically involve the meninges that surround the brain and spinal cord. Therefore, we describe the anatomy of the meninges in some detail.

Within the brain, sufficient arterial blood flowing in and venous blood draining out depends on pressure relationships between the three contents of the cranium:

- Blood
- CSF
- Brain tissue or parenchyma.

Changes in the pressure relationships between these components can result in serious and relatively common brain failures. At the same time, our ability to intervene and remedy, or at least ameliorate, conditions such as stroke, traumatic brain injury, hemorrhage, encephalitis, and **syncope**, or fainting, all depend on using an understanding of intracranial pressure to advantage.

THE BRAIN REQUIRES A STEADY AND CONSIDERABLE SUPPLY OF OXYGEN

The mammalian brain requires a disproportionately large proportion of the body's oxygen, about 25%, despite accounting for less than 3% of the body's mass. The delivery of oxygen to the brain is critical to brain function, so critical in fact that neurons show damage after seconds without oxygen and begin to die within minutes. *The brain suffers irreparable damage after only a few, less than 5, minutes without oxygen.* The heart, a runner-up to the brain in its oxygen requirement, continues to function for many minutes without oxygen.

Arterial blood flow to the brain, about 15%–20% of the heart's output, delivers oxygen to the threshold of the brain parenchyma, or tissue matter. Arteries dive into the brain, narrowing to arterioles and ultimately to capillaries. Oxygen diffuses out of cerebral blood vessels, while most nutrients are transported across the blood–brain barrier and into the parenchyma. Thus, **cerebral blood flow**, the flow of blood through cerebral arterioles and capillaries, is critical to the healthy operation of the brain. Cerebral blood flow in turn depends on **cerebral perfusion pressure (CPP)**, the pressure that drives blood through the cerebrum.

THE PRESSURE INSIDE THE RIGID CRANIUM LIMITS CEREBRAL PERFUSION PRESSURE

The brain needs oxygen and therefore needs adequate perfusion with oxygenated blood. Normally, the perfusion pressure in an organ is simply the arterial pressure that flows into the organ less the venous pressure that drains blood from the organ. Since an average mean arterial pressure (**MAP**) is 80–100 mm Hg or so and venous pressure is about 5–10 mm Hg, cerebral perfusion pressure would be 70–95 mm Hg, sufficient to adequately drive cerebral blood flow. This calculation assumes that the difference between the input and output pressures of the brain are all that impact cerebral perfusion pressure. However, in the case of the brain, there is an additional and critical factor: intracranial pressure (**ICP**) or the pressure caused by the rigid confines of the cranium. The contents of the cranium—blood, CSF, and parenchyma—exist at a pressure that is normally about 15 mm Hg.

Thus, intracranial pressure is greater than venous pressure. Consequently, intracranial pressure rather than venous pressure is subtracted from mean arterial pressure to calculate cerebral perfusion pressure, the pressure that drives cerebral blood flow through the brain:

$$\text{CPP} = \text{MAP} - \text{ICP}$$

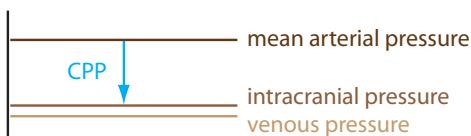
For adequate cerebral blood flow and oxygen delivery, cerebral perfusion pressure must be at least 60–80 mm Hg. A decrease in mean arterial pressure or an increase in intracranial pressure, potentially due to a tumor, swelling, or subdural hemorrhage, can produce a dangerous reduction in cerebral perfusion pressure and thereby cerebral blood flow (Fig. 14-1). At least some safeguards exist to ensure adequate, but not excessive, cerebral blood flow even as cerebral perfusion pressure varies.

CEREBRAL BLOOD FLOW IS HIGHLY REGULATED TO ENSURE THAT IT STAYS WITHIN PHYSIOLOGICAL RANGE

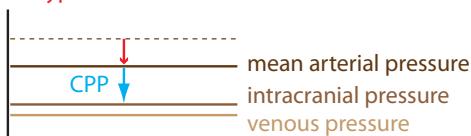
Autoregulation refers to a physiological mechanism by which the blood flow to an organ is protected from changes in systemic arterial pressure within a given range. Because of autoregulation, an organ's perfusion pressure stays constant, or at least within a working range, even as systemic blood pressure changes.

Figure 14-1. Cerebral perfusion pressure (CPP) depends on the difference between mean arterial pressure (MAP) and intracranial pressure (ICP). Venous pressure is not a factor, since it is consistently lower than intracranial pressure. Normally, arterial pressure is much greater than intracranial pressure (A) so that cerebral perfusion pressure (blue arrow) is adequate, >60 mm Hg. However when systemic arterial pressure plummets (red arrow), as in hypotension, the difference between arterial pressure and intracranial pressure decreases, so that cerebral perfusion pressure becomes inadequate (B). Similarly, when intracranial pressure is elevated (red arrow), for any of a variety of reasons, the difference pressure decreases and cerebral perfusion pressure is inadequate (C).

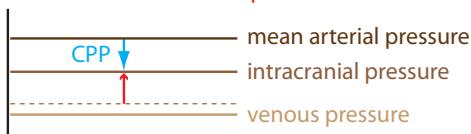
A. Normal: MAP >> ICP



B. Hypotension: MAP > ICP



C. Increased intracranial pressure: MAP > ICP

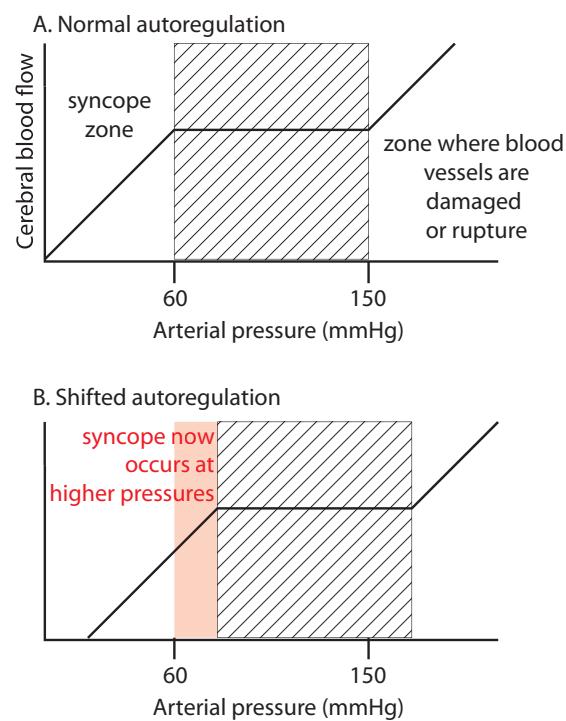


The range of arterial pressures tolerated and the mechanisms of autoregulation differ from organ to organ. In the case of cerebral autoregulation, cerebral blood flow, often abbreviated as CBF, is maintained at a steady level when the peripheral arterial pressure is between 60 and about 140–150 mm Hg. Thus, cerebral autoregulation ensures that the brain is supplied with sufficient oxygen and nutrients across a fairly large range of circumstances (Fig. 14-2). Cerebral autoregulation is achieved through two principal mechanisms:

- *Myogenic*: The smooth muscles surrounding arterioles are dilated in response to decreases in pressure and constrict in response to increases in pressure.
- *Metabolic*: Increases in carbon dioxide (CO_2) and decreases in oxygen (O_2) result in the dilation of arterioles and decreases in CO_2 result in the constriction of arterioles.

Consider the effect of each mechanism on cerebral blood flow. When blood pressure decreases, cerebral arterioles dilate, which serves to decrease resistance and thereby increase flow. When blood pressure increases, cerebral arterioles constrict, increasing vessel resistance and decreasing flow. *The myogenic contribution to cerebral autoregulation is the primary mechanism that keeps global cerebral blood flow within physiological limits.*

Figure 14-2. A: Normally, autoregulation keeps cerebral blood flow within physiological limits even as arterial pressure varies between about 60 and 150 mm Hg. If cerebral blood flow falls too low, syncope results, and if it rises too high, blood vessels, particularly small ones, are damaged and may even rupture. B: During periods of sustained elevations in blood pressure, as occurs during exercise or chronic hypertension, the range of autoregulation shifts to the right. This allows tolerance of higher pressures but it also puts an individual at increased risk of syncope because cerebral blood flow will be inadequate at pressures that are normally tolerated (shaded area).



Metabolic changes result from a number of factors, including neuronal activity. Active neurons generate CO₂ and utilize available O₂, leading to changes in local gas pressures. The increase in CO₂ and decrease in O₂ consequent to neuronal activity results in cerebral vessel dilation and hence, an increase in local blood flow. This is the principle upon which many modern imaging methods such as **functional magnetic resonance imaging**, or **fMRI**, are based. Conversely, vasoconstriction and a decrease in local blood flow follow a decrease in CO₂. The ultimate result of these metabolic autoregulatory reactions is that *cerebral blood flow is diverted from less active brain areas to more active brain areas*. In this way, metabolic influences on cerebral blood flow promote dynamic adjustments to local metabolic needs. The consequent change in the blood flow to different brain localities also means that local blood flow can deviate from the level defended by myogenic autoregulation in order to serve high levels of neuronal activity.

Myogenic and metabolic influences on cerebral blood flow maintain adequate rates of flow globally and locally in the face of both central changes in neuronal activity and peripheral changes in cardiovascular function. In addition to these autoregulatory mechanisms, the brain influences cerebral blood flow through additional pathways. For example, during exercise or during the clichéd conditions of “fight or flight,” activation of sympathetic neurons results in a shift of the range of autoregulation to higher pressure values (Fig. 14-2B). This shift allows tolerance of a higher range of systemic blood pressure. Chronic hypertension also shifts the range of cerebral autoregulation to the right much as sympathetic activation does. Although a rightward shift allows the brain to tolerate high blood pressures, it also increases the blood pressure threshold for insufficient cerebral blood flow. As a result, insufficient cerebral blood flow occurs when systemic pressure reaches values that are easily tolerated in normal healthy individuals at rest (Fig. 14-2B).

As the reader may imagine, there are circumstances when cerebral blood flow falls outside of the autoregulation range. When cerebral blood flow falls below the

Box 14-1

SYNCOPE RESULTS WHEN CEREBRAL BLOOD FLOW FALLS TOO LOW.

Syncope refers to a loss of consciousness accompanied by a loss of postural tone. A colloquial term for this combination is *fainting*. Note that a loss of consciousness can occur alone without falling, as it does during certain types of seizures, and a loss of postural tone without a loss of consciousness can also occur as in the case of **drop attacks**. Nonetheless, loss of both consciousness and postural integrity often occur together.

Syncope is a fairly common occurrence affecting about 10% of the population at one time or another. Cardiac problems such as hypotension or arrhythmia cause the vast majority of syncope cases with only about 10% initiated by a neural event such as a seizure. However, whatever the cause or trigger, even if cardiovascular in nature, syncope takes the form it does because of a global failure of cerebral function consequent to inadequate cerebral blood flow.

lower limit of autoregulation, about 60 mm Hg in healthy individuals, arterial perfusion of the cerebrum starts to decline with systemic blood pressure. Below about 30 mm Hg, cerebral blood flow stops. If cerebral blood flow falls too low and compensatory mechanisms such as increasing the rate of oxygen extraction fail, **syncope**, or fainting, occurs (see Box 14-1). When cerebral blood flow exceeds the upper limit of autoregulation, which happens at arterial pressures of about 140 or 150 mm Hg in nonexercising individuals, blood vessels can no longer maintain their resting tone and become passively dilated, resulting in damage to the vessel wall and potentially vessel rupture.

THE CIRCLE OF WILLIS CONNECTS BLOOD ARRIVING FROM TWO PAIRS OF MAJOR VESSELS

Arteries that supply blood to the brain enter through specific holes in the skull and circumnavigate the base of the brain in a characteristic pattern. The brain receives blood from two major sources (Fig. 14-3):

- The **posterior** or **basilar circulation** arises primarily from the **vertebral arteries** with a contribution from the **anterior spinal artery**. All three of the arteries supplying the posterior circulation enter the skull through the foramen magnum.
- The **anterior** or **carotid circulation** arises from the **internal carotid arteries**, which enter through the **carotid foramina** at the base of the skull.

The internal carotid arteries bring in about 70% of the circulatory input to the brain, with most of the remaining blood arriving via the vertebral arteries.

The anatomy of the arteries supplying the brain provides a major safeguard against inadequate cerebral perfusion. A continuous ring of arteries called the **Circle of Willis** connects the posterior and anterior circulations (Fig. 14-3). Because the anterior and posterior circulations are connected, the brain is fed by redundant blood supplies. This redundancy reduces the chance that the failure of one arterial source will render the brain **ischemic**, without blood supply, and therefore either **anoxic**, without oxygen, or **hypoxic**, with insufficient oxygen. For example, if one internal carotid artery becomes occluded, or blocked, the internal carotid on the other side can supply blood, and thereby oxygen.

The failure of a vessel to deliver blood to the brain is termed a **cerebrovascular accident** or **stroke** (see Box 14-2). Strokes are very common. They are in fact the most common neurological emergency and the number one neurological cause of death. Most strokes, about 85%, are ischemic due to the occlusion of a vessel. About 15% of strokes occur when a vessel ruptures, resulting in a hemorrhage.

The arterial supply to the brain contains numerous branch points where arteries divide or join together. The flow at these branch points is particularly turbulent, and the vessel wall is thin in some individuals due to either a genetic predisposition or

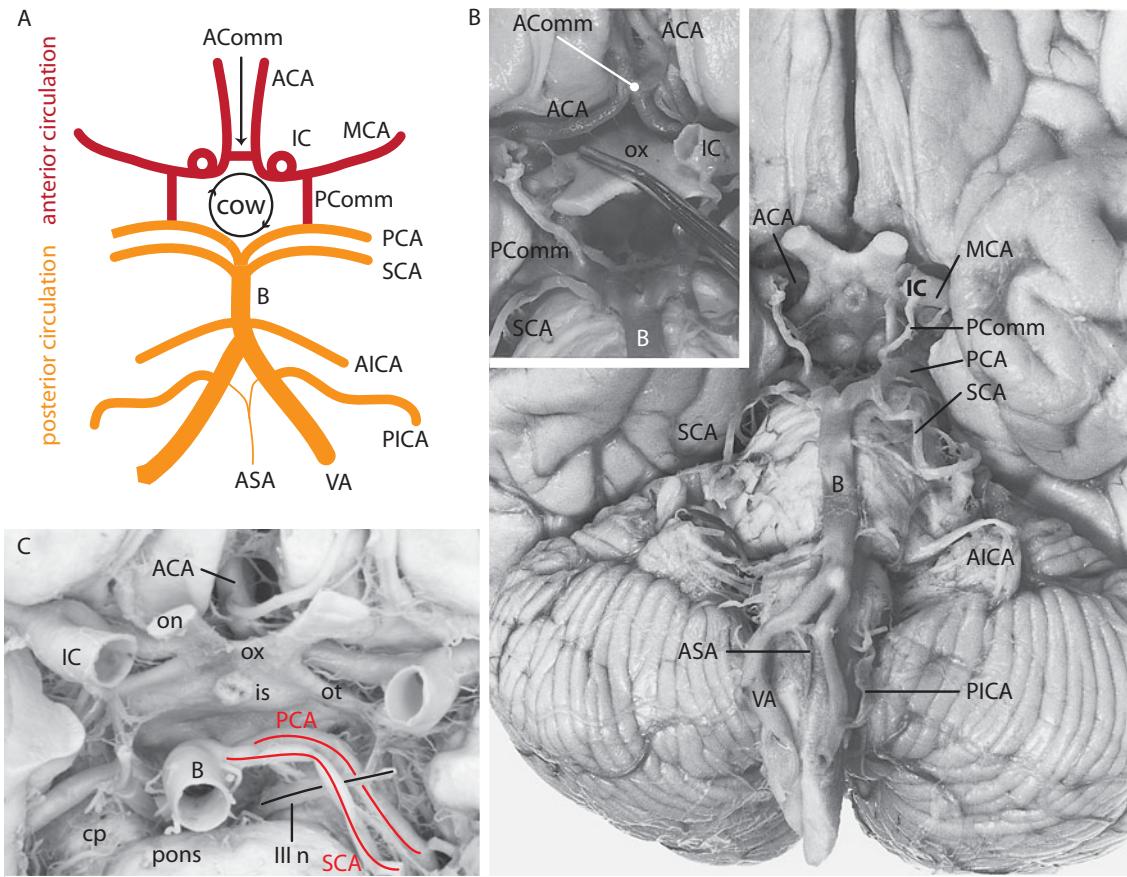


Figure 14-3. A: The blood supply to the brain is supplied primarily by the internal carotid (IC) and vertebral (VA) arteries. The main branches of the posterior or basilar circulation (orange) include the vertebral arteries, the anterior spinal artery (ASA), the basilar artery (B) and four sets of secondary arteries. The basilar artery is formed by the convergence of the two vertebral arteries. The posterior inferior cerebellar arteries (PICA) arise from the vertebral arteries, whereas the anterior inferior cerebellar arteries (AICA) and superior cerebellar arteries (SCA) come off the basilar artery. At the mesodiencephalic transition, the basilar artery splits into the two posterior cerebral arteries (PCA), the most anterior components of the posterior circulation. The main branches of the anterior circulation (maroon) include three communicating arteries and two pairs of cerebral arteries. The two posterior communicating arteries (PComm) link the posterior cerebral arteries to the middle cerebral arteries (MCA). The internal carotid, the major source of blood to the anterior circulation, splits into the middle and anterior (ACA) cerebral arteries. The two anterior cerebral arteries are connected by a single anterior communicating artery (AComm), which bridges the midline. The circle formed by the cerebral and communicating arteries, termed the Circle of Willis (circle labeled cow), allows for compensatory blood supply in the case of occlusion to one artery. B-C: The blood supply has a stereotypical relationship to the underlying brain and cranial nerves as the following examples illustrate. The caudal end of the basilar artery occurs at the pontomedullary junction, where the abducens nerve emerges at a site just behind the point where the anterior inferior cerebellar artery comes off the basilar artery (panel B). The optic chiasm (ox) sits in close proximity to the anterior cerebral and internal carotid arteries (B inset). The oculomotor nerve (III n) is sandwiched between the superior cerebellar artery and posterior cerebral artery (C). Additional structures labeled for orientation include the cerebral peduncle (cp), infundibular stalk (is), optic nerve (on), and pons.

Photographs in B and C reprinted with permission from Bruni, J.E., and Montemurro, D. *Human neuroanatomy: A text, brain atlas, and laboratory dissection guide*. New York: Oxford University Press, 2009.

to trauma. Where the arterial wall thins, outpouchings called **aneurysms** frequently develop. Under the best of circumstances, an aneurysm stays small and causes no problem, whereas under the worst of circumstances, an aneurysm ruptures, leading to an intracranial hemorrhage and a potentially deadly medical emergency (see Box 14-3).

STROKES OCCUR FOR A NUMBER OF REASONS.

Stroke refers to a heterogeneous group of cerebrovascular accidents that produce a sudden loss of brain function. About 80%–85% of strokes are **ischemic**, meaning that blood flow to a region of brain is interrupted. The remaining number of strokes results from the rupture of a cerebral vessel and the consequent hemorrhage, meaning leakage of blood into either the parenchyma or the space surrounding the brain. Different mechanisms underlie ischemic and hemorrhagic strokes; the latter are discussed in Box 14-3.

Brain tissue left without normal blood flow, either because of vessel occlusion or vessel rupture, dies. In addition, the area around an ischemic stroke, the **penumbra**, is in danger of dying. Stroke is a medical emergency, and *treatment is aimed at recovering function of as much of the penumbral area as possible*. Although stroke results in significant mortality, the good news is that patients who survive show significant improvement over time. It is not unusual, for example, for a person who becomes aphasic and paralyzed on the right side of the body to be able to talk and move, albeit with some subtle deficits, weeks to months later.

A common cause of ischemic strokes is an **embolus**, which is any matter that occludes a blood vessel. The composition of emboli (the plural of embolus) varies. A **thromboembolus** is composed of clotted blood that detaches from a vessel wall where it forms; the site of the clot formation is termed a **thrombosis**. An embolus may also be composed of material thrown off from an **atheroma** or **arthrosclerotic plaque**, a pathological collection of cholesterol, cells, and calcium that sticks to the walls of arteries. One of the risks associated with certain broken bones is that fat from the bone marrow will enter the circulation as **fat emboli** and clog small vessels in the brain.

Stroke can also result when an atheroma grows large enough to severely limit or even completely block flow through a cerebral artery. A final common cause of ischemic stroke is the occlusion of small vessels either from very small atheromata (plural

form), termed **microatheromata**, or from a process known as **lipohyalinosis**. In lipohyalinosis, the smooth muscle of an arteriole degenerates and is replaced by collagen, which narrows the opening of the arteriole, ultimately leading to thrombosis and occlusion. Whatever the cause of the small-vessel blockage, the result is a small area of damage, termed a **lacuna** (*lacunae* is the plural).

Ultimately, the circulatory system is to blame for ischemic strokes. Hypertension, smoking, diabetes, alcohol abuse, and a lack of exercise all adversely affect cardiovascular health and thereby greatly increase the risk of stroke. Although these risk factors can be ameliorated, additional risk factors, such as atrial fibrillation, are more difficult to address. In any case, odds are that an elderly, overweight smoker with diabetes and hypertension who experiences a sudden loss of the use of a limb, slurred speech, the ability to understand and use language, or the like has had a stroke.

The treatment of a stroke patient is two-pronged because, although the cause of stroke is a cardiovascular concern, the consequences are entirely neurological. First, treatment aimed at the cardiovascular system requires an understanding of the cause of a stroke. For example, drugs such as tissue plasminogen activator, that break down blood clots are used to restore blood flow in the case of certain types of ischemic stroke but obviously are ill-advised in the treatment of hemorrhagic stroke. Second, rehabilitative treatment for the neurological consequences of a stroke is tailored to the particular deficits experienced by each individual.

As stroke is the number one neurological cause of death, hospitalization, and serious illness, it is critical to understand both the cardiovascular and neurological contributions to this devastating and pervasive problem. Many if not most readers probably already know a friend or loved one who has experienced a stroke. Unfortunately, the chance of going through life without knowing someone—patient, friend, family member, or coworker—who has suffered a stroke is close to nil.

Box 14-3

BERRY ANEURYSMS OCCUR MOST COMMONLY AT SPECIFIC PLACES IN THE CIRCLE OF WILLIS AND BASILAR CIRCULATION.

A **berry**, or **saccular**, **aneurysm** is so named because it looks like a round sack attached to the artery by a thin stem. Berry aneurysms form preferentially at specific branch points in the Circle of Willis and in the posterior circulation. Often, berry aneurysms are asymptomatic. However, if they grow large enough, berry aneurysms can compress neighboring structures. More problematic is that berry aneurysms occasionally rupture. The resulting gush of blood produces an explosive headache and an often fatal increase in intracranial pressure.

THE POSTERIOR CIRCULATION SUPPLIES BLOOD TO THE BRAINSTEM AND CEREBELLUM

In the human, the vertebral arteries join to form the **basilar artery** at the junction between the pons and the medulla. Four important sets of bilateral arteries belong to the posterior circulation, one pair arising from the vertebral arteries and the remainder from the basilar (Fig. 14-3):

- Posterior inferior cerebellar arteries (**PICA**) come off the vertebral arteries.
- Anterior inferior cerebellar arteries (**AICA**) come off the basilar artery.
- Superior cerebellar arteries (**SCA**) come off the basilar artery.
- At its rostral end, the basilar artery splits into two **posterior cerebral arteries** (**PCA**).

Knowing the territories supplied by the major cerebral blood vessels is critical to understanding the symptoms that arise from a brainstem stroke. Most caudally, the posterior inferior cerebellar arteries emanate from the vertebral arteries to supply blood to the dorsolateral part of the caudal medulla and, as the artery's name suggests, to the posterior inferior part of the cerebellum (Fig. 14-4A). More anteriorly, the anterior inferior cerebellar arteries emanate from the basilar artery to supply blood to the dorsal part of the pons and the anterior inferior part of the cerebellum (Fig. 14-4B). Finally, at the pontomesencephalic junction, the superior cerebellar arteries emanate from the basilar artery to supply blood to the dorsal part of the midbrain and most of the convexity of the cerebellum (Fig. 14-4C). The basilar artery itself and the **paramedian penetrators** that come off of the basilar supply blood to the ventral and midline parts of the pons and midbrain (see Box 14-4). At its rostral pole, the basilar splits into two **posterior cerebral arteries**, and thereby forms the link between the posterior and anterior circulations.

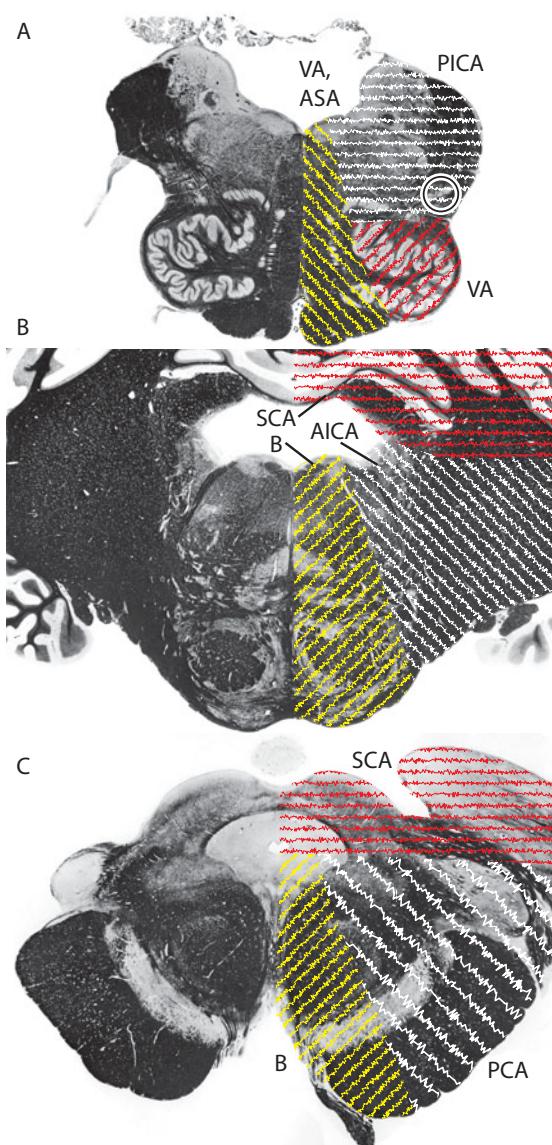
BLOOD FROM THE INTERNAL CAROTID ARTERIES REACHES THE FOREBRAIN

The anterior circulation receives oxygenated blood from the internal carotid arteries, which supply 70%–80% of the Circle of Willis blood volume. Along with the posterior cerebral arteries from the posterior circulation, two additional pairs of cerebral arteries and three communicating arteries comprise the anterior circulation that completes the Circle of Willis:

- Two **anterior cerebral arteries** (**ACA**)
- Two **middle cerebral arteries** (**MCA**)

Figure 14-4. The blood supply to the brainstem is supplied by a mixture of at least six prominent arteries. In the medulla (A), the most medial regions receive blood from small offshoots called paramedian penetrators, which come off of the anterior spinal (ASA) and vertebral (VA) arteries. Ventrolaterally, the inferior olive receives blood from the vertebral artery and the dorsolateral medulla receives blood from the posterior inferior cerebellar artery (PICA). The location of the sympathoexcitatory tract from hypothalamus to thoracic sympathetic neurons is marked by a circle on the right, within the territory of the posterior inferior cerebellar artery. Interruption of this tract, as occurs in lateral medullary strokes, produces Horner syndrome. The most medial portions of both the pons (B) and midbrain (C) receive blood from paramedian penetrators arising from the basilar artery (B). B: Lateral parts of pons receive blood from the anterior inferior cerebellar artery (AICA). Note that the superior cerebellar peduncle, along with most of the convexity of the cerebellum (not shown) receives blood from the superior cerebellar artery (SCA). C: Ventrolateral midbrain receives blood from the posterior cerebral artery (PCA), whereas dorsal midbrain and caudal parts of thalamus receive blood from the superior cerebellar artery.

Photomicrographs reprinted with permission from deArmond S., et al. *Structure of the human brain: A photographic atlas*. New York: Oxford University Press, 1989.



- One anterior communicating artery (AComm)
- A pair of posterior communicating arteries (PComm)

The Circle of Willis consists of the ring formed by the three communicating arteries and the proximal sections of the six cerebral arteries (Fig. 14-3A). A large degree of congenital variability in the Circle of Willis exists across individuals, with up to 75% of the population possessing some variation on the standard circle.

Each internal carotid splits into anterior and middle cerebral arteries. The two anterior cerebral arteries travel forward and supply the medial face of each cerebral hemisphere (Fig. 14-5). Between the two anterior cerebral arteries, there is the small—actually tiny—anterior communicating artery. The middle cerebral artery dives through the Sylvian fissure to provide blood to most of the convexity of the brain (Fig. 14-5). On the way laterally, it gives off lenticulostriate arteries that supply

MOST BRAINSTEM STROKES IMPAIR SOMATOSENSATION AND VOLUNTARY MOTOR CONTROL.

Understanding the neurological symptoms that will result from damage in different regions of the central nervous system is an excellent review of neuroanatomy. The reader who is able to predict the deficits that occur after damage to a defined area is one who successfully grasps the essentials of neuroanatomy.

The two most common brainstem strokes are Wallenberg syndrome (see Box 12-7) and medial pontine strokes. In Wallenberg syndrome, or lateral medullary syndrome, recall that the most common symptoms result from damage to the most superficially placed structures in the lateral medulla. Before looking at the answers below, look back at Figures 12-3, 12-4, 12-5, and 12-6. What tracts are present most laterally? What nucleus is present most laterally? What symptoms would you predict from damage to these structures?

Here are the answers. The structures most commonly damaged, and the symptoms produced by that damage, are:

- The restiform body, leading to ataxia and abnormal eye movements
- The vestibular nuclei, leading to vertigo, nausea, and abnormal eye movements
- The caudal portion of the spinal trigeminal tract and nucleus, leading to abnormal pain and temperature sensation in the ipsilateral face

- The spinothalamic tract, leading to loss of pain and temperature sensation in the contralateral body.

A lateral medullary stroke usually also produces ipsilateral ptosis and miosis due to Horner syndrome (see Box 9-3). In this case, Horner syndrome results not from an interruption of the peripheral pathway from the thoracic cord to the eye but from damage to an excitatory pathway from the hypothalamus to preganglionic sympathetic neurons in the thoracic cord (see Box 12-7). This excitatory pathway travels in the lateral medulla very near to the spinothalamic tract (Fig. 14-4).

Medial pontine strokes, typically lacunar in nature, damage the basis pontis, usually on one side. Consequently, the most common symptoms are hemiplegia, affecting the control of muscles of the body and lower face, contralateral to the site of damage. As a result, people are unable to willfully move their arms or legs, to make purposeful facial expressions, and often have dysarthria. All of these symptoms result from interruptions of the descending corticospinal and corticobulbar tracts.

Large pontine strokes that produce locked-in syndrome, described in Chapter 1, are, thankfully, rare.

the caudate, putamen, globus pallidus, and posterior limb of the internal capsule. Since the corticospinal tract travels in the posterior limb of the internal capsule, it is useful to remember that the source of blood and oxygen for this structure is the middle cerebral artery. Upon reaching the Sylvian fissure, the middle cerebral artery splits into inferior and superior divisions supplying the temporal lobe and parietal lobe convexity, respectively. Two posterior communicating arteries connect the middle and posterior cerebral arteries. The posterior cerebral arteries provide blood to the ventral temporal lobe and the occipital lobe, including visual cortex (Fig. 14-5).

Although strokes affecting the anterior circulation are highly varied, the most common strokes produce classic sets of symptoms (see Box 14-5). The location of more unusual strokes can be logically deduced from the observed symptoms.

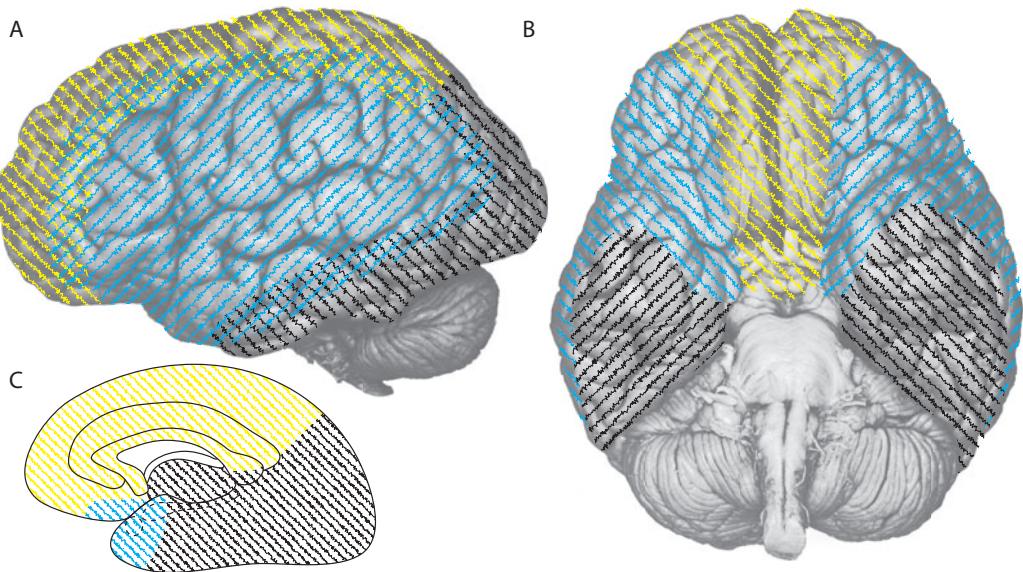


Figure 14-5. A-C: The blood supply to the forebrain derives principally from the anterior, middle, and posterior cerebral arteries. The middle cerebral artery (blue lines) supplies the largest territory, including most of the cerebral convexity (A). The anterior cerebral artery (yellow lines) supplies blood to most of the medial surface of the brain, all except the most posterior regions (C). The posterior cerebral artery (black lines) supplies blood to the caudal portions of the brain and to the ventrum of the temporal lobe (B). Watershed zones occur where the blood supplies from two cerebral arteries overlap, as occurs extensively on the cerebral convexity (A). In the event of hypotension, a sensory and motor loss in the trunk and proximal limbs results from lack of perfusion in the more anterior of the watershed zones, between the anterior and middle cerebral arteries. This causes the so-called “man in the barrel” syndrome. Loss of perfusion in the posterior watershed zone, between the middle and posterior cerebral arteries, produces a deficit in the contralateral visual field. As it travels laterally, the middle cerebral artery gives off small tributaries, the lenticulostriate arteries, which supply blood to the striatum and posterior limb of the internal capsule. This is important as the posterior limb of the internal capsule carries the corticospinal tract, with arms represented most anteriorly and legs most posteriorly. Upon reaching the Sylvian fissure, the middle cerebral artery splits into two divisions. The inferior division supplies the temporal lobe, whereas the superior division supplies the parietal and frontal convexities.

Photographs in A and B reprinted by permission of deArmond S., et al. *Structure of the human brain: A photographic atlas*. New York: Oxford University Press, 1989.

ANASTOMOSES PROVIDE SAFEGUARDS AGAINST OXYGEN DEPRIVATION

Anastomoses are interconnections between capillaries arising from different parent arteries. Extensive networks of anastomoses exist on the convexity of the brain at the junctions of the anterior and middle cerebral arteries and of the middle and posterior cerebral arteries (Fig. 14-5). The region of brain supplied with blood by an anastomosis is termed a **watershed zone**. Since watershed zones receive blood from two major arterial systems, one can compensate for the other in cases of blockage. For example, if the middle cerebral artery is occluded, the motor cortex serving the proximal leg, trunk, and proximal arm muscles is spared from harm as it can derive sufficient blood supply from the anterior cerebral artery. Watershed zones have their down side as well. Since anastomoses occur at the terminal ends of arteriolar domains, watershed zones are most vulnerable to hypoxia consequent to low cerebral blood flow when blood pressure is low.

Small penetrating vessels that arise from major vessels of both the anterior and posterior circulations and do not communicate with any other blood vessels are the

CEREBRAL STROKES PRODUCE STEREOTYPICAL SYNDROMES.

Strokes in the anterior circulation most often occur in the middle cerebral artery or one of its tributaries. A stroke in the middle cerebral artery **stem**, meaning before the artery has branched, has numerous and severe consequences. Recall that the middle cerebral artery provides blood to most of the brain's convexity. As a result, the following structures can be damaged:

- Primary motor cortex
- Primary sensory cortex
- Optic radiation
- Frontal eye fields

Damage to these four regions produces contralateral hemiplegia, loss of contralateral sensation and sometimes contralateral dysesthesia, contralateral homonymous hemianopia, and a loss of the ability to willfully look to the contralateral side. In addition, if the stroke occurs in the dominant hemisphere, the left one in most people (see Chapter 13), aphasia will result. A complete stroke of the middle cerebral artery in the nondominant hemisphere may impair prosody (see Chapter 17) and will produce contralateral hemispatial neglect (see Chapter 16). Strokes in tributaries of the middle cerebral artery will produce some subset of the above damage and respective symptoms. For example, one of the most common strokes involves sudden onset Broca's aphasia and right face and arm paralysis, a constellation of symptoms that is

pathognomonic for a stroke in the superior division of the left middle cerebral artery. Lacunar strokes often plague the lenticulostriate arteries, causing contralateral weakness due to interruption of the blood supply to the posterior limb of the internal capsule where corticospinal tract fibers travel.

Strokes in the posterior or anterior cerebral arteries cause more restricted damage as the brain territories supplied are smaller. Often, the only deficit resulting from a posterior cerebral artery stroke is contralateral homonymous hemianopia, an inability to see the contralateral visual field using either eye. Smaller strokes within the posterior cerebral artery territory cause smaller, but always homonymous, visual field deficits. With larger strokes that reach the diencephalic territory supplied by the posterior cerebral artery, pathways to and from the primary somatosensory and motor cortices may be interrupted, impairing contralateral somatosensation and voluntary movement.

Recall that the anterior cerebral artery supplies blood to the medial wall of the frontal and parietal lobes and extends, over the wall, to supply blood to the very dorsal part of the cerebral convexity (Fig. 14-5). Since the legs are represented medially in both somatosensory and motor cortex, a stroke in the anterior cerebral artery causes paralysis of and a loss of sensation from the contralateral feet and legs. Additionally, as large regions of prefrontal cortex receive blood from the anterior cerebral artery, impaired social competence, incontinence, and other behavioral symptoms may also occur.

opposite of anastomoses. The brain regions supplied by such terminal vessels are referred to as **end zones**. Lenticulostriate arteries are examples of terminal vessels.

THE FLUID-FILLED SACK FORMED BY THE DURA AND ARACHNOID PROTECT THE BRAIN FROM MECHANICAL DAMAGE

The dura and arachnoid, the two outer meninges, serve to protect the brain from mechanical trauma by encasing the brain in a fluid-filled sack. The outermost membrane, the dura, is the toughest (dura is Latin for *hard*)

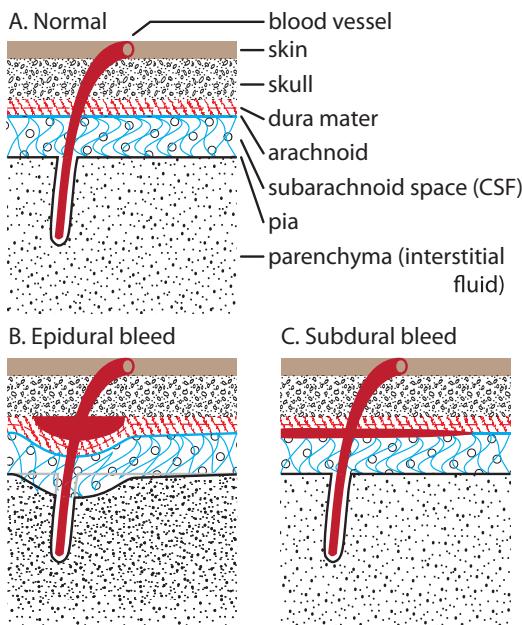
meningeal membrane. The arachnoid, the middle meningeal membrane, adheres tightly to the inside of the cranial dura. Both the dura and arachnoid follow the curvature of the skull rather than the sulci and gyri of the brain. Thus, the overall shape of the outer two meninges essentially forms an endocast of the brain cavity. Between the arachnoid and the brain, the **subarachnoid space** is filled with CSF (Fig. 14-6A). The arachnoid connects to the pia via gossamer-like **trabeculae**, or filaments, and the pia borders brain parenchyma. Under ideal circumstances, the dura, arachnoid, and CSF-filled subarachnoid space comprise the protective sack of fluid that prevents the brain from **traumatic** or mechanical impact. However, blows to the head that are strong enough or directed at particularly vulnerable areas of the skull, as well as skull-penetrating wounds that overwhelm meningeal protection, cause **traumatic brain injury** (see Box 14-6).

There are two dural layers:

- The outer **periosteal layer** of the dura affixes to the inside of the skull bone throughout the cranium.
- The inner **meningeal layer** of the dura adheres tightly to the periosteal layer except in two places where it doubles up to form dural folds.

Two folds of dura form an internal armature that strengthens the integrity of the sack formed by the dura and arachnoid. The two folds are the falx cerebri and the tentorium cerebelli, commonly referred to as simply the tentorium. The falx cerebri forms a divider separating the right and left cerebral hemispheres dorsal to the corpus callosum (Fig. 14-7A-B). The tentorium, interposed between the occipital cortex and the cerebellum, partitions the cranium into a **supratentorial fossa** and an

Figure 14-6. The three meningeal layers protect the brain from traumatic injury and maintain the chemical milieu of the brain. The dura adheres to the skull, and the arachnoid adheres to the dura. The pia adheres to the brain parenchyma. Consequently, there is a space between the arachnoid and the pia, the subarachnoid space, which is filled with cerebrospinal fluid (CSF). The arachnoid includes trabeculae, thin filaments, that link the arachnoid membrane superficially to the pia below. These spidery filaments are the root of the name arachnoid, which derives from the Latin word for cobweb. There are two potential spaces within the cranial meninges. These spaces should not contain fluid and only do so under pathological conditions. Blood vessels traverse the meninges and can rupture either epidurally or subdurally. Epidural bleeds occupy the potential space between the unyielding skull and the dura (B). Subdural bleeds occupy the potential space between the dura and arachnoid (C).



BLOWS TO THE HEAD CAN DAMAGE THE BRAIN BOTH AT THE SITE OF THE TRAUMA AND ELSEWHERE.

A strong enough or particularly aptly placed blow to the head can cause traumatic brain injury, often abbreviated as TBI. Damage may occur superficially at the site of impact, termed a **coup** injury, at a site directly opposite to the impact, termed a **contrecoup** injury, or at both sites. For example, a blow to the front end of the brain may damage frontal brain regions, the coup injury, and also occipital brain regions, the contrecoup injury. Traumatic impacts with rotational force, such as a right hook, tend to produce deeper injuries that often involve axonal shearing.

Traumatic brain injury causes effects that range from mild and transient to severe and permanent and, ultimately, in many cases to death. Traumatic brain injuries with immediate and severe consequences—death or permanent impairment—are typically due to a percussive blow or a penetrating wound. At the other end of the spectrum, the mildest form of traumatic brain injury, commonly termed a **concussion**, is a reversible impairment of cognitive function that many people experience at some time in their life. A concussion may result immediately in mental confusion, such as not knowing one's location, a period of unconsciousness, a brief episode of amnesia, and so on. The long-term consequences can be more serious. Even TBIs that appear mild initially, may wreak severe damage after a delay. Furthermore, repeated TBIs, even ones which produce no or only mild effects on their own, can result in permanent symptoms including amnesia,

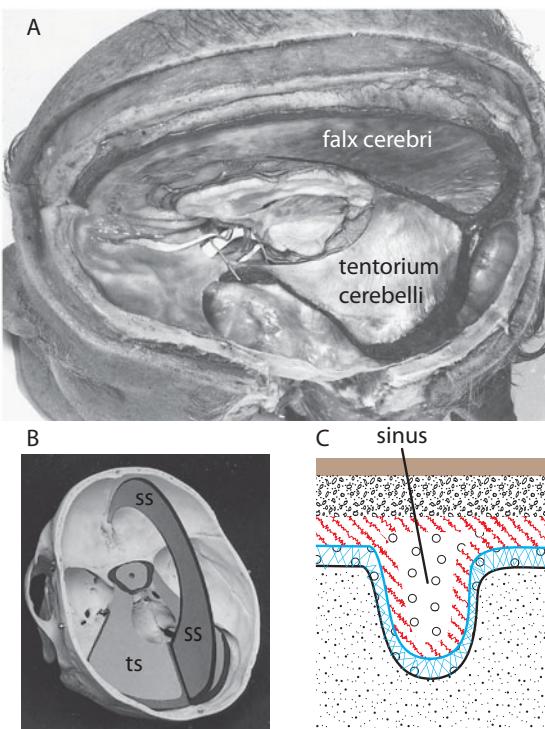
seizures, dementia, and parkinsonism. For example, **dementia pugilistica** is a condition with all of the above symptoms that is prevalent among former boxers. Recently, the debilitating effects of repeated mild concussions, or even simply hits to the head, in American football players have been brought to light.

The mechanism by which TBI causes brain dysfunction involves pathological changes at the cellular and molecular levels that follow an initial mechanical impact. The secondary reaction to the primary trauma defines the outcome and presents the most opportune target for therapeutic intervention. After the initial impact, a number of destructive molecular events can occur including increases in free radicals, excitotoxicity, and excess nitric oxide release. These pathological changes conspire to promote apoptosis, or programmed cell death, among neurons and glia and **cytotoxic edema** or pathological cell swelling. The blood-brain barrier may be compromised by a traumatic impact (see more in Box 14-9). When combined with cytotoxic edema, a compromised blood-brain barrier often leads to severely reduced cerebral blood flow and a failure of autoregulation. Managing cerebral perfusion pressure is the major macroscopic intervention available currently, whereas therapies aimed at rendering the molecular environment as hospitable to recovery as possible are our hope for the future.

infratentorial fossa (Fig. 14-7B). The forebrain is wholly supratentorial, whereas the hindbrain is infratentorial. The partitions formed by the falx cerebri and tentorium lend some protection to one compartment if pressure builds in the other compartment, akin to the protection formed by bulkheads in a ship's hull. Thus, the tentorium and falx cerebri restrict the damage inflicted by a localized **mass**, trauma, or swelling. Of course, the separation promoted by the falx cerebri and tentorium are insufficient in the face of a large enough mass or a large enough elevation in intracranial pressure, either of which can cause the brain to **herniate** (see Box 14-7).

Figure 14-7. A: Two large folds of dura present in the human cranium are shown in a dissected head. The falx cerebri separates the two hemispheres and the tentorium cerebelli separates the occipital cortex from the cerebellum. When the intracranial pressure builds up sufficiently, mass effect can substantially deform the brain (see Box 14-7). B: Within each fold of dura are venous sinuses. As diagrammed on this model, the tentorium contains the transverse sinus (ts) and the falx contains the sagittal sinuses (ss). The upper rim of the falx houses the superior sagittal sinus, and the lower rim contains the inferior sagittal sinus. C: Sinuses are formed by a separation between the outer and inner layers of the dura. Two inner layers of dura fold up to contain a sinus.

Photographs reprinted with permission from Bruni, J.E., and Montemurro, D. *Human neuroanatomy: A text, brain atlas, and laboratory dissection guide*. New York: Oxford University Press, 2009.



Box 14-7

HERNIATION RESULTS FROM A FAILURE OF INTRACRANIAL PARTITIONING.

Mass is the term used for any space-occupying entity in the brain. A mass can be a tumor, blood from a hemorrhage, or simply parenchymal swelling. The pressure caused by a mass, of whatever makeup, can build up to a point at which the gross shape of the brain changes; such a deformation of the brain is termed **mass effect**. The most subtle mass effect is **effacement**, meaning simply a smoothing of cortical convolutions. Far more dramatic examples of mass effect are when brain tissue no longer stays on the normal side of the falx cerebri or tentorium. In such situations, a piece of the brain **herniates** or slips under the dural fold.

Uncal herniation occurs when the **uncus**, the anterior part of the parahippocampus gyrus, slips under the tentorium. Uncal herniation is a very dangerous form of herniation as a herniated uncus presses on the brainstem. Therefore, uncal herniation is lethal unless quickly remedied. The first sign of uncal herniation is typically a “blown pupil,”

meaning a pupil that is both dilated and unresponsive. This results from the herniated uncus compressing the third nerve as it exits the ventrum of the midbrain. Uncal herniation also causes loss of consciousness due to compression of midbrain regions critical to arousal. Additional types of brain herniation may occur on their own or in combination with other types. **Central herniation**, a form of transtentorial herniation like uncal herniation, is marked by parts of forebrain slipping under the tentorium at a site close to the midline. **Tonsillar herniation**, often secondary to either uncal or central herniation, is extremely dangerous as the cerebellum slips outside of the foramen magnum. Finally, the most common form of herniation is **subfalcine**, in which some portion of the cingulate gyrus slips under the falx cerebri. Although not always harmful or even symptomatic when occurring alone, a subfalcine herniation may be a harbinger of more consequential damage.

THE INTEGRITY OF THE MENINGES IS ESSENTIAL FOR THE CHEMICAL PROTECTION OF THE CENTRAL NERVOUS SYSTEM

Beyond providing mechanical protection, the meninges also provide a chemical barrier that prevents large molecules from entering the CNS. The chemical barrier is formed deep to the arachnoid in the innermost meningeal layer, the pia mater. Pia follows every sulcus and gyrus and every bump and crevice in the cerebral surface. Thus, pia is covered by the CSF-filled subarachnoid space and in turn, pia blankets the brain surface situated deep to it.

To review, as we traverse from the outside to the inside of the head, we encounter the skull, periosteal layer of the dura, meningeal layer of the dura, arachnoid, subarachnoid space filled with CSF, pia, and finally brain parenchyma (Fig. 14-6A). Ideally, the only fluid-filled space between skull and parenchyma should be the subarachnoid space interposed between pia and arachnoid, and the only fluid in this space should be CSF. No other spaces between bone and parenchyma *should* exist. All other spaces are *potential spaces*, meaning that they can be, but definitely should *not* be, filled with fluid. *In other words, potential spaces are actual fluid-filled spaces only under pathological conditions.* The two potential spaces are:

- The **epidural space**, sometimes called **extradural**, is the potential space between the outer periosteal layer of the dura and the *skull* (Fig. 14-6B).
- The **subdural** space is the potential space between dura and arachnoid (Fig. 14-6C).

Cutting across all layers from periosteal dura to pia are blood vessels, arterial and venal, which import oxygen and nutrients to the brain and remove waste products from the brain, respectively (Fig. 14-6A). Arterial vessels arrive from the periphery and penetrate the arachnoid and pia to provide oxygen and nutrients to the parenchyma. Venous blood is collected into sinuses formed by folds of dura and then emptied into veins that exit into the periphery. As blood travels in and out through the meninges, ripe opportunity exists for blood to accidentally leak into one of the potential or actual spaces. Blood leaking out from cerebral vessels, due to trauma or a number of other reasons, is a potentially life-threatening occurrence (see Box 14-8).

When blood hemorrhages within the cranium, it fills any of four spaces:

- *Epidural*: a potential space in the cranium that *should not contain fluid*
- *Subdural*: a potential space that *should not contain fluid*
- *Subarachnoid*: an actual space that should contain CSF and *not blood*
- *Parenchymal*: brain tissue that should contain **interstitial** fluid, a fluid that is not different from CSF, and should definitely *not* contain blood.

INTRACRANIAL BLEEDS ARE POTENTIALLY LETHAL AND SHOULD BE TREATED AS MEDICAL EMERGENCIES.

Hemorrhages, or bleeds, often occur after a traumatic injury such as a blow to the head, a fall that results in hitting the head, or a whiplash. Bleeds can also occur without any obvious precipitating trauma, as when an aneurysm or an arteriovenous malformation bursts or because of medical conditions such as hypertension. The amassed blood or **hematoma** usually causes sudden symptoms with the patient complaining of a severe headache that arose explosively.

Bleeds can occur into one or more of four spaces:

- An **epidural hematoma** is blood amassed between the dura and the skull, usually due to a blow to the side of the head (Fig. 14-6B). An epidural hematoma is a serious medical emergency as it typically results in death if not treated. The onset of symptoms such as a loss of consciousness may coincide with the onset of the epidural bleed or may follow a **lucid interval**, a period without symptoms during which blood presumably amasses to a dangerous and symptomatic level.
- A **subdural hematoma** is blood amassed between the dura and the arachnoid (see Box 14-12 below and Figure 14-6C). It can follow a traumatic injury but can also occur spontaneously in elderly people. Some small subdural hematomas shrink over time and are not life-threatening.
- Rupture of a berry aneurysm (see Box 14-3) or of an arteriovenous malformation and trauma are the most common causes of **subarachnoid hemorrhage**. Blood is released into the subarachnoid space between the arachnoid and pia, a space that should only contain cerebrospinal fluid. Components of blood, such as serotonin, strongly stimulate trigeminal afferents that innervate the vasculature itself. The activation of

trigeminal nociceptors produces a particularly severe and sudden headache that is described as the worst ever or the worst imaginable. With time, a subarachnoid hemorrhage compromises an individual's mental status, creating mental confusion, a loss of consciousness, and sometimes death. Thus, subarachnoid hemorrhage is a medical emergency and must be treated immediately. Treatments are directed at preventing more bleeding by, for example, clipping an aneurysm and also at preventing **vasospasm**. Vasospasm refers to a pathological constriction of cerebral vessels that occurs after the vessels have been exposed to blood. It is important to prevent the development of vasospasm in order to avert the ischemia that results from pathologically constricted blood vessels. Even when treatment is attempted, the prognosis for individuals with subarachnoid hemorrhage is often poor.

- A **parenchymal hemorrhage** is a bleed into brain tissue that results from trauma or from strokes associated with conditions such as hypertension, a brain tumor, or an arteriovenous malformation. The symptoms of a cerebral hemorrhage are largely dependent on the location of the bleed and the functions supported by the affected brain tissue. As with most other intracranial bleeds that increase intracranial pressure, a cerebral hemorrhage is a medical emergency. Pharmaceutical treatments are aimed at reducing bleeding and swelling, whereas surgical procedures relieve intracranial pressure.

Hopefully, the reader understands the important take-home message: *any severe headache or compromise to mental status with a sudden onset should be taken very seriously and treated as a medical emergency until proven otherwise.*

A parenchymal, alternatively termed *intracerebral*, bleed occurs when blood leaks directly into brain tissue. Intracerebral hemorrhages are harmful both because they increase intracranial pressure *and* because they permit entry to substances normally excluded from the CNS by the blood–brain barrier.

THE BLOOD–BRAIN BARRIER ENSURES A SPECIFIC CHEMICAL ENVIRONMENT FOR THE CENTRAL NERVOUS SYSTEM

The CNS exists in a distinct molecular environment from that of the rest of the body. This distinct environment is maintained by the blood–brain barrier or BBB. Brain endothelial cells line capillaries to form this barrier, which keeps extracellular molecules of certain sizes and characteristics out of the brain. The capillaries that actualize the blood–brain barrier are densely distributed throughout the brain, so that *virtually every cell has its own private access to a capillary*. In fact, it has been estimated that there are *400 miles* of capillary in the brain of a *mouse*!

The lining of peripheral blood vessels is imperfect and leaky, allowing free exchange of blood between vessel and tissue. In contrast, capillaries in the brain and spinal cord are surrounded by *unfenestrated* endothelial cells that are connected to each other via tight junctions. Unfenestrated simply means that the capillary wall is effectively continuous; no gaps exist between the endothelial cells lining the capillary. Cerebral blood vessels allow free diffusion of gases including oxygen, water, and some small amphiphilic substances that access the brain by crossing directly through membranes. However, bacteria, parasites, fungi, white blood cells, red blood cells, platelets, and the like cannot enter the brain. Moreover, molecules beyond about 50 kD in size, including antibodies and many potentially therapeutic drugs, are unable to move from brain capillaries into the parenchyma. *Therefore central and peripheral chemical environments are largely distinct.*

There are exceptions to the rule that large molecules do not enter the CNS. A small number of molecular transporters carry specific classes of molecules across the vessel wall and into brain. Of particular importance are transporters that bring glucose and various amino acids into the brain. Specific channels allow critical ions access to the CNS. The upshot of the blood–brain barrier is that *peripheral blood is filtered into a clear, watery fluid with no cells, very little protein, about 65% of the glucose present in blood, and nearly the same concentrations of ions as blood*. This clear, watery fluid is the extracellular fluid, also called interstitial fluid, that bathes the cells of the brain.

The blood–brain barrier works both for us and against us. The barrier helps us by keeping out toxins, bacteria, and antibodies against endogenous antigens. Yet, the blood–brain barrier also keeps out many potentially helpful, therapeutic compounds. Furthermore, a breakdown in the blood–brain barrier may initiate, accelerate, or contribute to the pathology of a number of neurological disorders including Alzheimer’s disease, Parkinson’s disease, and multiple sclerosis (see Box 14-9).

THE BLOOD–BRAIN BARRIER CHANGES UNDER PATHOLOGICAL CONDITIONS.

Many central nervous system pathologies are accompanied by a compromised blood–brain barrier. For example, vessels supplying brain tumors typically lack a tight barrier. A compromised blood–brain barrier may play a key role in the pathology of some diseases afflicting the central nervous system (CNS). In autoimmune diseases such as multiple sclerosis and stiff person syndrome, antibodies that should not reach the CNS gain access, presumably through a breakdown in the blood–brain barrier. Recent work

suggests that β -amyloid protein, which accumulates to pathogenic levels in patients with Alzheimer disease, is not cleared from the brain of affected individuals. The cause-and-effect relationship between disease and blood–brain barrier dysfunction is not well established. Thus, it may be that a failure in blood–brain barrier function is a causal factor in disease. Alternatively, disease progression may cause blood–brain barrier failure and then in turn be accelerated by the same.

CEREBROSPINAL FLUID BATHES THE ENTIRE CENTRAL NERVOUS SYSTEM

Arterial blood filtered through the blood–brain barrier forms the interstitial fluid that bathes the brain parenchyma. Because of the filtering, the composition of the fluid in the extracellular space of the CNS is different from that of both blood and extracellular fluid in the body. Yet, extracellular fluid within the CNS exchanges freely with, and is therefore *not different* in composition from the CSF that fills the ventricles and surrounds the brain and spinal cord (Fig. 14-8A).

Like the extracellular fluid in brain, CSF is a clear, watery fluid that is made by filtering blood. In the case of CSF, the blood–CSF barrier present in choroid epithelium acts as the filter. As choroidal epithelial cells are not neuronal, they are located outside the CNS, but since they service the CNS they line its edges (see Chapter 3). Thus, wherever you see choroid plexus, the choroid epithelium side borders a ventricle and the arteriole side is outside of the brain.

Recall that choroid epithelium forms a complex, termed choroid plexus, with incoming arterioles (see Box 3-7 and Fig. 3-5). Arterial blood enters the choroid plexus and is filtered by the unfenestrated choroidal epithelial cells to form CSF, just as the blood in capillaries is filtered by capillary endothelial cells to form the interstitial fluid bathing the brain. Choroid plexus is present in five places (Fig. 14-8B):

- Roof of the lateral ventricle, bilaterally
- Roof of the third ventricle
- Posterior-lateral region of the fourth ventricle, bilaterally

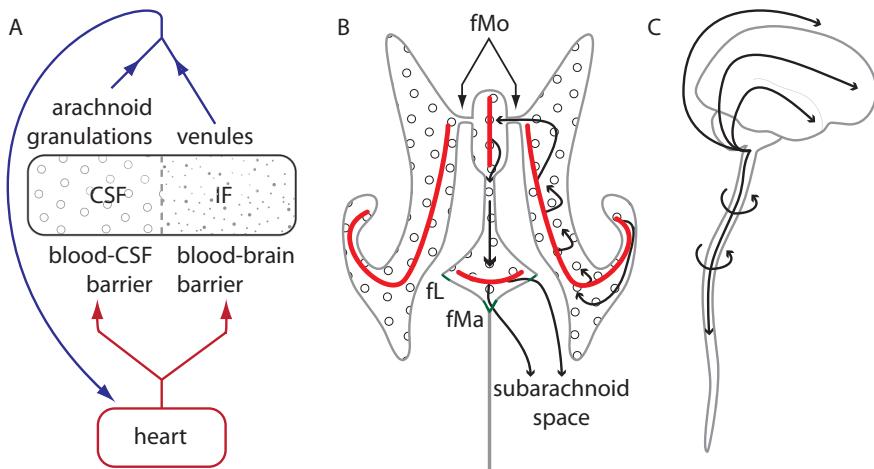


Figure 14-8. Arterial blood from the heart enters the brain parenchyma only after traversing the blood–brain barrier. Within the parenchyma, blood that has been filtered through unfenestrated endothelial cells becomes the interstitial fluid (IF) of the brain. Blood also enters the brain through capillaries in the choroid plexus. The choroid plexus forms a blood–cerebrospinal (CSF) barrier. Yet, there is no separation between CSF and brain interstitial fluid. Thus, both barriers—in parenchymal capillaries and in the choroid plexus—are typically called the blood–brain barrier. Venules receive the waste of the brain parenchyma, and arachnoid villi and granulations transport CSF into dural sinuses. Venous blood then returns to the general circulation. **B:** Non-neuronal choroidal epithelial cells adhere to capillaries to form choroid plexus (red lines), which borders the lining of the lateral, third, and fourth ventricles. Choroid plexus is easily identified by its irregular appearance (see top of the section in Fig. 14-4A). Choroid plexus secretes CSF at a rate of half a liter, or more than two cups, per day. The bulk of the CSF in the human brain is made within the lateral ventricles. Once formed, CSF flows (black arrows) through the ventricular system. Cerebrospinal fluid made within the lateral ventricles traverses the foramen of Monro (*fMo*) to reach the third ventricle. Cerebrospinal fluid leaves the ventricular system through three holes in the fourth ventricle, the bilateral foramina of Luschka (*fL*, only one side is labeled), and the midline foramen of Magendie (*fMa*). Note that this diagram is the same as that in Figure 3-3G, where the parts of the ventricular system are labeled. **C:** Cerebrospinal fluid escaping from the back of the fourth ventricle bathes the subarachnoid space surrounding the brain and spinal cord.

Box 14-10

THE PRESENCE OF WHITE BLOOD CELLS AND PROTEIN IN CEREBROSPINAL FLUID (CSF) REVEALS AN INFECTION OF THE BRAIN AND MENINGES.

Meningitis is an infection of the meninges, and **encephalitis** is an infection of brain parenchyma. In either case, the CSF of an affected individual will have an abnormal increase in white blood cells. A lumbar puncture is typically used to diagnose meningitis. Whether caused by a bacterium or a virus, meningitis causes a headache, heightened sensitivity to sounds and light, fever, and a painful, stiff neck.

The cerebral aqueduct has no choroid plexus, thus lowering the risk of obstructing its small opening.

Although choroid plexus is found throughout the ventricular system, most CSF is made in the lateral ventricles. Consequently, CSF flows out from the lateral ventricles, through the foramina of Monro, to fill the third ventricle (Fig. 14-8B). Cerebrospinal fluid from the lateral ventricles, along with CSF made by choroid plexus in the roof of the third ventricle, then flows caudally through the narrow, Sylvian aqueduct present in the midbrain. As midbrain gives way to hindbrain, CSF flows into the large rhomboid-shaped fourth ventricle. More CSF is made by choroid plexus in the caudal roof of the fourth ventricle. From the fourth ventricle, CSF leaks out to the subarachnoid space surrounding the brain's convexities through three holes—the midline **foramen of Magendie** and the lateral **foramina of Luschka**. Cerebrospinal fluid that exits the fourth ventricle flows up and around the convexity of the brain and also flows caudally to surround the spinal cord and spinal roots (Fig. 14-8C). Recall from Chapter 9 that a pool of CSF termed the **lumbar cistern** surrounds the cauda equina and that we can sample CSF through a lumbar puncture (see Fig. 9-7C) at this level of the spinal column (see Box 14-10). A lumbar puncture can also be used to test the pressure within the dural sac which is elevated during conditions of **hydrocephalus** (see Box 14-11).

SEVERAL VENTRICLE-LINING AREAS HAVE A COMPROMISED BLOOD-BRAIN BARRIER, ALLOWING THE BRAIN ACCESS TO CERTAIN SYSTEMIC SUBSTANCES

Arterioles leading to fenestrated capillaries supply five CNS regions which consequently have an incomplete blood-brain barrier. Leaky areas include the posterior or neural pituitary (see Chapter 13) and five circumventricular organs:

- Subfornical organ
- Organum vasculosum of the lamina terminalis (OVLT)
- Subcommissural organ
- Median eminence
- Area postrema

Box 14-11

HYDROCEPHALUS IS TREATED WITH A NEUROSURGICAL SHUNT.

Hydrocephalus, commonly referred to as “water on the brain,” is any impairment of cerebrospinal fluid (CSF) flow through the ventricles, into the subarachnoid space, and then out of the cranium. In most cases, an obstruction to CSF flow results in an increase in ventricular CSF and then in ventricular pressure, leading to enlarged ventricles and ultimately to an increase in intracranial pressure. Pediatric hydrocephalus, a relatively common problem, occurs for a number of reasons, such as birth defects that block CSF flow. For example, *Chiari malformations* are a heterogeneous group of structural abnormalities that often occlude the flow of CSF out of the fourth ventricle and into the subarachnoid space. Cerebrospinal fluid builds up and, if untreated, affected babies will develop an unusually large head. When hydrocephalus occurs early enough in development, a baby’s **fontanelles**, the soft junctions between cranial bones, may fail to close and bulge out due to the excess intracranial pressure. Babies with hydrocephalus fail to thrive, showing lethargy, poor appetite, and vomiting along with a characteristic enlarged head.

Hydrocephalus is treated with the neurosurgical insertion of a shunt that brings CSF from the ventricles

to the atrium or peritoneal cavity. Shunts typically have a valve that permits CSF flow out of the brain when a pressure threshold is exceeded. Patients with hydrocephalus typically require *life-long* shunting. Unfortunately, a shunt can malfunction, become infected, or simply fail, and when it does, there will be a renewal of the symptoms of hydrocephalus. The frequency of shunt failure is revealed by the fact that only a minority of shunt operations for hydrocephalus represent the first such operation for the patient. In other words, patients undergo repeated shunt “fix-ups” through their lifetime.

In developing countries, a single neurosurgical operation is fiscally and logically difficult to arrange, and circumstances make multiple operations extremely unlikely. Therefore, the preferred approach in developing countries is to perform an **endoscopic third ventriculostomy**, which means creating a hole between the third ventricle and the subarachnoid space of the **interpeduncular cistern**, a pool of CSF located between the cerebral peduncles. This procedure has the advantage that no foreign material, subject to infection, is introduced into the brain.

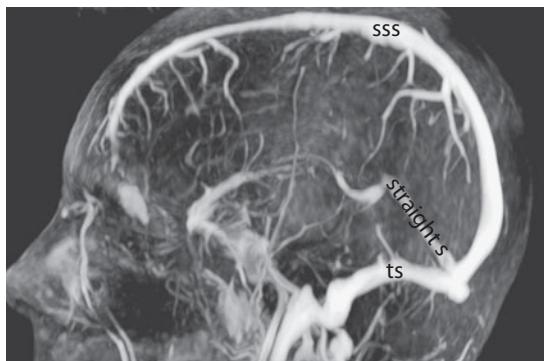
Each of these regions serves a particular function that requires access to and monitoring of blood contents. For instance, the subfornical organ monitors the blood levels of **angiotensin**, a liver hormone, in order to maintain homeostatic water balance. The area postrema monitors blood for certain **emetic**, or vomit-inducing, substances. In response to, for instance, hypotonicity, activation of area postrema neurons leads to vomiting. The organum vasculosum of the lamina terminalis monitors blood for fever-producing substances, called **pyrogens**, and engages fever production when pyrogens are detected.

Circumventricular organs are isolated from the rest of the brain by **tanycytes**, ependymal cells that are connected by gap junctions. Thus, even the substances that reach circumventricular organs do not have free access to the brain's extracellular space and thence to the CSF circulation.

BLOOD AND CEREBROSPINAL FLUID FEEDS INTO SINUSES EN ROUTE TO VENOUS DRAINAGE OUT OF THE CEREBRUM

Within the brain, extracellular fluid returns to venous blood through capillary venules, whereas CSF is transported from the subarachnoid space directly into sinuses (Fig. 14-9). Sinuses are pockets formed by folds in the dura (Fig. 14-7C) and filled with venous blood. Within the falk cerebri, there are two sagittal sinuses: the **superior sagittal sinus** receives blood from the superficial cerebrum, and the **inferior sagittal sinus** receives blood from deeper parts of the cerebrum (Fig. 14-7B). Veins collect venous blood from the venules and shuttle it into sinuses via bridging veins that cross the subarachnoid space and flow into the sinuses (see Box 14-12). For example, blood from the thalamus and basal ganglia drains into the **great vein of Galen**, which empties into the inferior sagittal sinus, which eventually becomes the **straight sinus** (Fig. 14-9). The straight sinus drains into the **transverse sinus**, which continues into the **sigmoid sinus**, and then into the

Figure 14-9. This angiogram shows the major sinuses and veins that drain venous blood and cerebrospinal fluid (CSF) from the brain. Abbreviations: straight sinus (*strights*); superior sagittal sinus (*sss*); transverse sinus (*ts*). Photograph reprinted with permission from Bruni, J.E., and Montemurro, D. *Human neuroanatomy: A text, brain atlas, and laboratory dissection guide*. New York: Oxford University Press, 2009.



A RUPTURE OF BRIDGING VEINS IS THE MOST COMMON CAUSE OF A CHRONIC SUBDURAL HEMATOMA.

Bridging veins shuttle venous blood from the parenchyma to the dural sinuses. They travel straight out from the brain, like spokes on a wheel, to the dura where the veins are anchored firmly. However, the bridging veins are not well anchored at the brain side (Fig. 14-10). Therefore, when the brain moves within its dural sack, the bridging veins are stretched. When the brain moves side-to-side, the falk cerebri limits the excursion traveled by the brain and therefore the potential of tearing the bridging veins. However, when the brain moves forward and backward, such as occurs during a whiplash or when a baby is shaken, the bridging veins are in particular danger of breaking. When bridging veins rupture, they usually do so at their thinnest spot, which is between the dura and the arachnoid, producing a subdural hematoma.

A subdural hematoma caused by rupture of bridging veins often bleeds slowly—remember that venous pressure is low—and may take weeks to become symptomatic. In fact, some proportion of individuals with a subdural hematoma never seeks medical attention either because the hematoma is resorbed or because it never grows large enough to cause symptoms.

As we age, our brain shrinks and this stretches the bridging veins, which also become more brittle with age. Consequently, the elderly are at a heightened risk of developing chronic subdural hematomas. Babies who are shaken, as occurs in abusive and criminal anger, are at risk of developing acute subdural hematoma, which is an often fatal medical emergency.

jugular vein. The spot where the superior sagittal, straight, and transverse sinuses come together is termed the **confluence of the sinuses**.

Cerebrospinal fluid from the subarachnoid space joins venous blood in the sinuses. Minute volumes of CSF are endocytosed by arachnoid prominences termed **villi** when small, or **granulations** when larger. Arachnoid granulations absorb a vacuole of CSF, transport it across the cell, and release it into a sinus.

Figure 14-10. A: Bridging veins exit from the parenchyma at a right angle, traverse the arachnoid, and attach firmly (circle) to the dura. B: When a person is shaken vigorously, particularly in the anterior-posterior axis, the brain moves within the dural sack. The bridging veins stretch and often break at their thinnest point, between the arachnoid and the dura. Rupture of bridging veins is the most common cause of subdural hematomas. Note that the space between the dura and arachnoid is microscopic and has been greatly exaggerated for illustrative purposes.

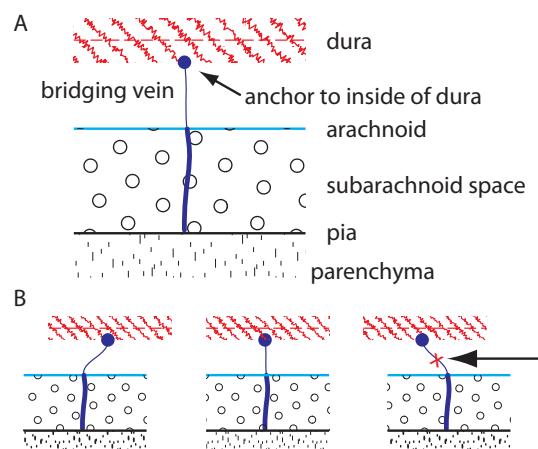
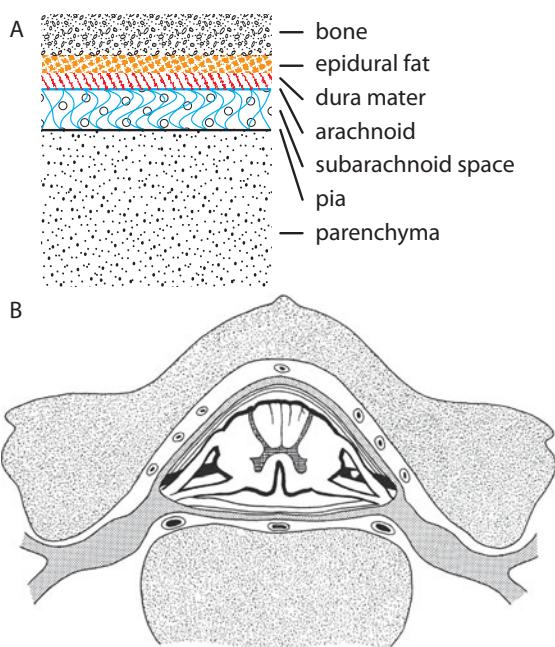


Figure 14-11. The meningeal covering of the spinal cord differs from that of the brain in one key way. The dura surrounding the spinal cord does not adhere to the bone of the vertebral column. Instead, a layer of epidural fat is interposed between bone and dura. As a result, the epidural space, which is a potential space in the cranium, is an *actual* space in the spinal cord.

Diagram in B reprinted with permission from Bruni, J.E., and Montemurro, D. *Human neuroanatomy: A text, brain atlas, and laboratory dissection guide*. New York: Oxford University Press, 2009.



Box 14-13

SPINAL EPIDURALS
ARE GIVEN INTO
THE ACTUAL
EPIDURAL SPACE
THAT EXISTS
IN THE SPINAL
COLUMN BUT NOT
IN THE CRANIUM.

Spinal epidurals, used for pain relief during child birth and medical procedures, are given into the epidural space between the vertebral column and the periosteal layer of the dura surrounding the spinal cord (Fig. 14-11). Note that this space is present in the spinal column but not in the cranium since cranial dura affixes directly to the skull periosteum.

THE LACK OF A RIGID VAULT MAKES DELIVERY OF NUTRIENTS AND REMOVAL OF WASTE FROM THE SPINAL CORD STRAIGHTFORWARD

The spinal cord derives its blood supply from the vertebral arteries that arise from the subclavian arteries. In turn, the vertebrals supply the anterior spinal artery that supplies the anterior two thirds of the spinal cord. The anterior spinal artery is less a proper artery, distinct from others, and more a hodge-podge of anastomoses. Segmental arteries give rise to **radicular arteries** that circle the spinal cord and anastomose with both anterior and **posterior spinal arteries**. The posterior spinal artery supplies blood to the posterior third of the spinal cord.

The meninges are somewhat differently arranged within the vertebral column. The periosteal layer of dura does not attach to the vertebral bones as it does to the cranium (Fig. 14-11). Instead, there is a layer of fat, termed **epidural fat**, interposed between the periosteal layer of dura and the vertebral bones (see Box 14-13). As it is not contained in a rigid casing, the spinal cord is not under pressure, as the brain is. Therefore perfusion pressure is simple: arterial pressure less venous pressure. Spinal strokes can happen, but fortunately only rarely.



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SECTION 4: PERCEPTION

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CHAPTER 15

PERCEIVING THE WORLD

Sensing the outside world is critical to both survival and reproduction. Moreover, sensory systems prevent us from being individual islands, enabling us to fulfill our social destinies. Sensory pathways work at an unconscious level to guide our movements, provide necessary information to homeostatic systems, and influence our mood. Thanks to sensory systems, we avoid walking into trees, we sweat when our body temperature increases, and looking at a beautiful sunset makes us feel happy. As illustrated by these examples, sensory systems operate automatically, outside of voluntary control or awareness, in many circumstances. Yet, sensory systems also allow us to gain *awareness* of our surroundings and our insides. The conscious awareness of either our environment or our own bodies that arises from activity in sensory pathways is termed *perception*.

In this section, we focus on the perceptual aspects of sensation. Visual, auditory, and somatosensory perception are of obvious importance to humans, and a chapter is devoted to each of these systems. We also devote a chapter to the vestibular system because the unpleasant symptoms that occur when the vestibular system stops working—vertigo, dizziness, nausea—hammer home the importance of the vestibular sense to our conscious life. We give short shrift to gustation, olfaction, and certain types of somatosensation such as proprioception. Rather than funneling into perception, these sensory systems contribute to unconscious functions such as maintaining balance, controlling motor force, or regulating the speed of ingestion, topics that will be discussed within those contexts in later sections.

TRANSDUCTION, TRANSMISSION, AND MODULATION ARE COMPONENTS OF ALL PERCEPTUAL PATHWAYS

The starting point for all sensation is a **stimulus**, meaning any change in the external environment or internal milieu. To transform a stimulus into perception, the brain uses pathways that share a common blueprint. Every perceptual pathway includes three predominant processing stages (Fig. 15-1):

1. Transduction refers to the conversion of some kind of stimulus energy, such as light or mechanical displacement, into a neural signal.

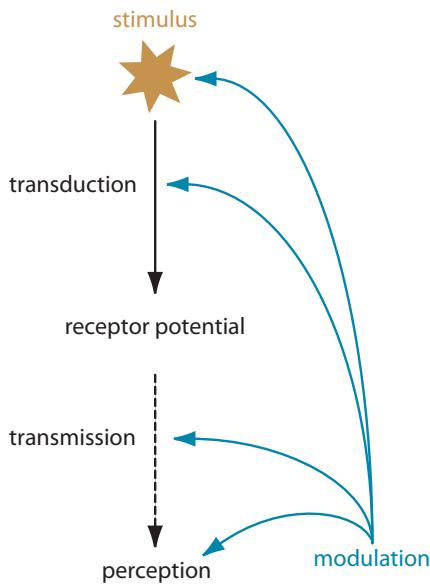


Figure 15-1. Sensory pathways leading to perception include three components: transduction, transmission, and modulation. The transduction of a stimulus into a receptor potential by a sensory receptor cell is a necessary first step in translating a stimulus into perception. Transmission carries the information regarding the stimulus through the nervous system to the cerebral cortex, the seat of perception and other cognitive functions. Stimulus information, carried by central neurons in the form of a series of action potentials, is refined as transmission ascends the neuraxis. Modulation can operate at multiple levels of the sensory pathway, from the periphery to the cerebral cortex to modify the neural interpretation of a stimulus, allowing different perceptions to result from the same physical stimulus under different circumstances.

2. Transmission carries the signal from the site of transduction to the cortex through an **oligosynaptic** pathway, meaning a pathway involving several synapses.

3. Modulation acts on transmission pathways at multiple levels, allowing context to modify sensation.

In order to sense the world either inside or outside of our bodies, we use sensory receptors to transform various types of energy into an electrical potential interpretable by the nervous system. For example, as discussed in Chapter 8, photoreceptors transduce or convert light energy into a change in membrane potential. Mechanically sensitive sensory receptors are involved in sensing touch, sound, head acceleration and position, and organ distension. Examples of the latter include **baroreceptors** that sense blood pressure and afferents sensitive to mechanical deformations that sense bladder fullness. **Chemoreceptors**, cells with specific receptors that respond to certain chemicals, are critical to smell, taste, pain, and to visceral sensations, such as the partial pressure of oxygen in the blood.

After transduction, sensory information is transmitted from the site of the sensory receptor, up the neuraxis, to the cerebral cortex. All sensory information except olfactory input makes a stop in thalamus before reaching cerebral cortex (see Chapter 13). When transmission of sensory information reaches the cerebral cortex, perception can occur. Although we do not entirely understand the mechanisms that give rise to perception, the experience of neurosurgical patients who receive intraoperative brain stimulation while awake provides compelling evidence that the cerebral cortex is in fact responsible for perception (see Box 15-1).

Sensory pathways from stimulus to cerebral cortex are modulated, in a myriad of ways, by both local and descending influences. An example of local modulation is the mutual inhibition between two inputs that enhances the detection of stimulus edges. Another example is the **Land effect**, in which light of a single wavelength is interpreted as different colors depending on the wavelengths emitted from surrounding objects. Modulatory processes are also responsible for rendering the feel of an ice cold drink as pleasurable on a hot day and unpleasant on a frigid winter day.

STIMULATION IN SENSORY CORTICES ELICITS CONSCIOUS PERCEPTIONS.

During neurosurgical procedures to remove an epileptic focus or a tumor, patients are often treated with local anesthetics and remain awake. The local anesthetics prevent the patient from feeling pain from the scalp, skull, and dura. Since there are no somatosensory receptors in the brain itself, brain stimulation itself does not cause pain. Therefore, neurosurgeons perform surgeries on awake patients. This approach helps neurosurgeons ensure that they do not damage language areas.

So, what happens when the brain is electrically stimulated? An extremely interesting general account of the effects of cortical stimulation is given in *The Cerebral Cortex of Man* by Penfield and Rasmussen (1950). In general, there are a limited number of outcomes to brain stimulation:

- Report of a sensation: “I feel a sensation in my hand” or “I see flashing lights in front of me.”
- Simple movements like those made by a baby, a feeling of not being able to move, or a feeling of wanting to move: The neurosurgeon may see flexion or extension of a joint or the patient may report, “You paralyzed my hand” or “my hand wants to shake,” or “my hand and arm contracted.”
- Interpretation of a scene: “I hear an orchestra playing.”

- Report of a memory or scene: “I heard an old friend call my name.”
- Aphasia: To test for aphasia, a neurosurgeon may ask a patient to count during the procedure. A Broca’s-type aphasia is observed when the patient stops speaking. Afterward, the patient reports “you paralyzed my jaw” or something to that effect. To reveal other types of aphasia, a neurosurgeon may show a common item and ask the patient to name it. Stimulation may prevent the patient from speaking or from naming the object. For example, Penfield and Rasmussen reported that a patient shown a top said, “one of those things that goes” during stimulation. When stimulation ended, the patient immediately said “top.”

For our purposes here, the important outcome is the first listed. Sensory perceptions reliably occur when a region of sensory cortex is stimulated. Often the sensations are abnormal. For example, patients report sensations of tingling or pins and needles rather than a squeeze of the arm or a gentle breeze. The abnormal sensations are likely the result of the artificial excitation of neurons by electrical stimulation. The neurons excited by an electrode are those that are closest to the electrode and not necessarily those that would be excited by a natural stimulus under normal, physiological conditions.

SENSE ORGANS STEER STIMULI TO SENSORY RECEPTORS

In order for transduction to occur, stimulus energy must reach a sensory receptor. We possess specialized organs that guide stimulus energy toward appropriate sensory receptors, meaning receptors that are able to transform the type of stimulus energy gathered into a receptor potential. Thus, the eye focuses light onto the retina, where photoreceptors transduce light into a change in membrane potential. Sniffing transports volatile odorants into the nose, where they can bind to sensory receptors. Ingestion and chewing distribute **tastants**, meaning substances that we taste, so that they can reach taste cells within oral tastebuds. After information about

a stimulus reaches a sensory receptor, transduction occurs through mechanisms specific to each type of afferent. Transduction mechanisms for vision, hearing, somatosensation, and vestibular senses will be discussed in the following chapters. Importantly, *a stimulus only registers to the extent that we possess the machinery to transduce that stimulus into a neural potential.*

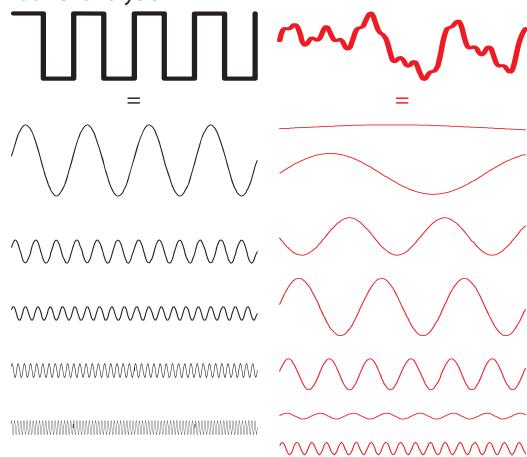
The type of energy transduced by a sensory receptor reflects sensory function in some but not all cases. Clearly, the conversion of light into a hyperpolarization by photoreceptors allows us to sense the visual world. Thus, light transduction and photoreceptor function align well. In contrast, mechanically sensitive sensory neurons called *hair cells* in the ear transduce mechanical displacements of less than a micron rather than the larger movements caused by sound and head motion. In other words, hair cells are sensitive to physical displacements that are thousands of times smaller than the physical movements caused directly by sound, head position, or head acceleration. It is the apparatus surrounding the hair cells that is responsible for transforming sound or head motion into mechanical displacements of less than a micron.

THE BRAIN PROCESSES SENSORY STIMULI USING A FOURIER-TYPE ANALYSIS

Fourier analysis is a powerful tool in sensory physiology as it allows us to break up complex stimuli into simple components. The basic idea behind Fourier analysis is that any signal consists of a number, oftentimes a large number, of component sinusoidal waves. Static noise, a pure musical tone, and clicks can all be reproduced by summing a finite number of sinusoidal waves with specific frequencies, amplitudes and phases (Fig. 15-2A). Similarly, a picture has high, medium, and low spatial frequency components (Fig. 15-2B–D) and a movie has both spatial and temporal frequency components. In visual terms, low spatial frequencies convey the proverbial forest, the general scene, whereas high spatial frequencies are critical to our perception of the trees, the detail. The same tool of Fourier analysis can be applied to vestibular stimuli.

The fundamental idea that visual, auditory, vestibular, and mechanical stimuli can be represented as the sum of a number of sinusoids is important because the nervous system appears to use a form of Fourier analysis to process sensory signals. One example of this principle in the periphery is the distribution of different component frequencies in a complex sound to different locations in the cochlea (see Chapter 17). The result is an auditory prism whereby auditory frequencies are mapped along the length of the cochlea. Fourier-type analysis also occurs in sensory pathways of the central nervous system. For example, high spatial frequency information is used for high-acuity vision, important in reading and perceiving the form of objects, whereas low spatial frequencies are most important for detecting moving objects. Damage or disease within central visual pathways can preferentially impair high- or low-spatial-frequency vision.

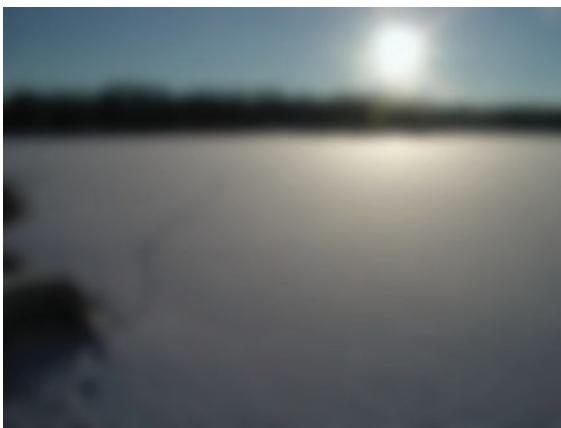
A. Fourier analysis



B. Original photograph of winter scene: all frequencies



C. Winter scene: low frequencies only



D. Winter scene: high frequencies only



Figure 15-2. Using Fourier analysis, stimuli can be represented by the addition of a finite number of sinusoidal waves. A: Fourier analysis can reveal the component sine waves within a periodic signal, such as a square wave (left), as well as in nonperiodic noise (right). The bolded signals in the top traces can be formed by the addition of the sine waves below the equal signs. B–D: Most natural scenes contain a mixture of low and high spatial frequencies. Low-frequency components within the original image in B are shown in panel C, and high-frequency components are illustrated in D. Note the differences between the low- and high-frequency components in different features. Details, such as the fox tracks, the branch in the bottom left foreground, and the outline of tree tops, are primarily high spatial frequency features. Most of the color in this image is at low spatial frequency. Some features have both low- and high-frequency components that are prominent. For example, the sun has a high spatial frequency edge and a low spatial frequency change in color and luminance.

Photograph in B kindly provided by Gisèle Perreault.

SENSORY RECEPTORS RESPOND PROBABILISTICALLY TO A RANGE OF STIMULI

Receptors do not react to the entire spectrum of possible environmental stimuli. Humans cannot see the infrared emissions coming from a warm body, hear the ultrasonic vocalizations of bats, or navigate through the environment by sensing electric fields. Yet, these are biologically possible senses: some snakes perceive infrared emissions, bats and other animals detect ultrasound, and sharks navigate and find prey by sensing the electric field. Different animals have evolved

different complements of sensory receptors, each of which responds to a certain range and type of stimulus. For example, we possess receptors that respond to vibrations centered at about 300 Hz, or light of about 500 nm in wavelength, or temperature around 37°C.

The activation of a receptor is probabilistic, meaning that stimuli with certain characteristics are most likely to excite the receptor, whereas stimuli with similar but not identical properties also excite the receptor but with lower probability (Fig. 15-3). A **tuning curve**, such as that in Figure 15-3A, shows the combination of stimulus intensity and feature—wavelength, frequency, temperature, and the like—which are needed to excite a receptor. Such a tuning curve can be constructed for all sensory

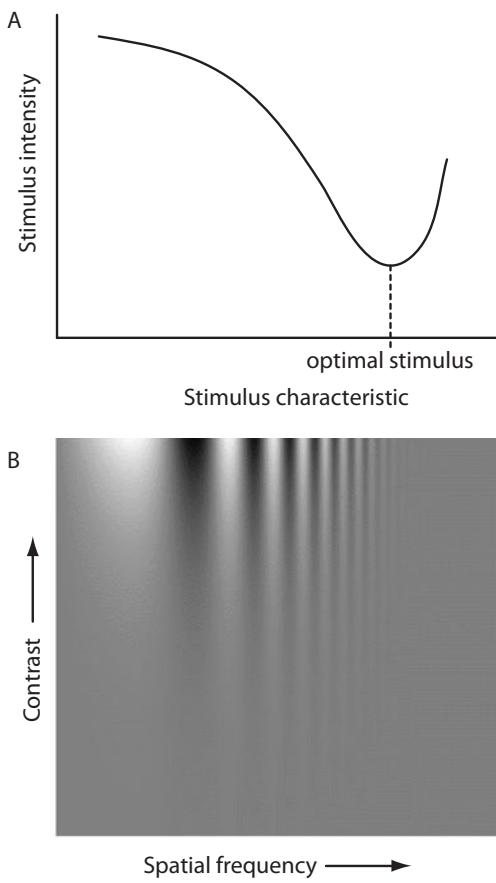


Figure 15-3. A: A stereotypical tuning curve for a sensory receptor is shown. The stimulus intensity needed to excite the sensory receptor at each value of the appropriate stimulus property is plotted. For example, the amount of light, in candles or some other measure of light intensity, needed to excite a photoreceptor is least at a given wavelength, the optimal wavelength. Light at other wavelengths may excite the photoreceptor, but there is a greater chance of excitation as the intensity of light at a nonoptimal wavelength increases. Note that sensory receptors are often named for the stimulus that excites them at minimal intensity, their optimal stimulus; as an example, cone photoreceptors that respond to short wavelength light are called short-wavelength cones. Note that the tuning curve is not a step function but has some width. Consequently, sensory receptors respond to a range of stimuli. For many sensory receptors with broad tuning curves, the probability of activation does not decrease rapidly as a stimulus characteristic deviates away from the optimal value. B: A black-and-white grating with continuously varied contrast (vertical direction) and spatial frequency (horizontal direction) illustrates the relationship between an optimal stimulus feature and intensity. The stimulus feature is spatial frequency and the intensity varies with contrast. At optimal spatial frequencies, gratings are visible even at low contrast. However very-high-frequency gratings (all the way to the right) are not visible at any contrast level. Very-low-frequency gratings (all the way to the left) are only visible at high contrast values. If you draw a line at the boundary between the part of the gratings visible to you and the part that is at too low of a contrast to perceive, the shape of that line will be similar to that of the tuning curve in A.

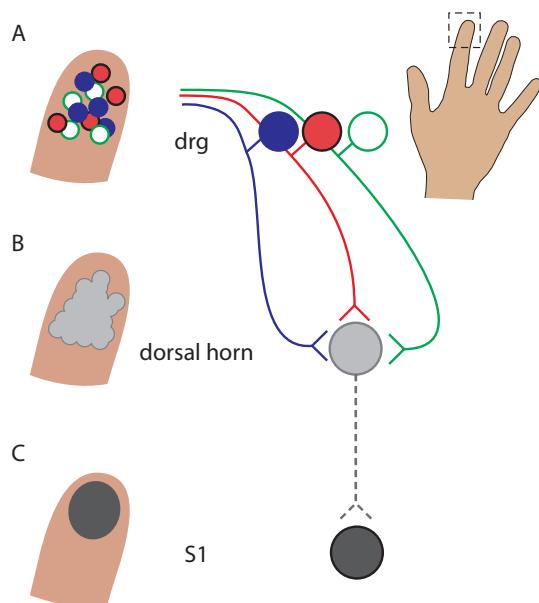
Panel B kindly provided by S. Murray Sherman.

receptor types. Consider for example the **Pacinian corpuscle**, which is a type of somatosensory afferent that reacts to vibration. Pacinian corpuscles respond optimally to vibration at 300 Hz, meaning that vibration at 300 Hz will excite Pacinian corpuscle even when the skin is indented only by a minute amount. Pacinian corpuscles are also excited by vibration at frequencies other than 300 Hz, but require that the skin is indented more than in the case of the 300 Hz vibration. Thus, the stimulus intensity, meaning amount of indentation, needed to excite Pacinian corpuscles is minimal at the optimal frequency of vibration and greater at other vibration frequencies.

Every sensory receptor responds to stimulation in some locations but not others. The range of locations where appropriate stimulation will excite a sensory receptor is termed the **receptive field**. For example, some cutaneous somatosensory afferents respond to indentation of the skin at the tip of the index finger (Fig. 15-4) but not the tip of the thumb, whereas other afferents have reciprocal properties. Some cells in the auditory pathway respond to sound arising from a particular location in space (see Box 15-2). Light from a specific region of the visual field hits photoreceptors, and that region of space is the photoreceptor's receptive field. The small receptive fields of somatosensory afferents and photoreceptors summate to form larger, smoother, and better delineated receptive fields as sensory transmission ascends the neuraxis (Fig. 15-4).

Since sensory receptors operate by probability, one might expect that perceptions will be misleading in some small proportion of cases. If a photoreceptor that responds optimally to short wavelength light may, on rare occasion, respond to light of medium wavelength, then why don't we perceive the blue sky as green every long once in a while? To understand why we never see the sky as green, consider that the receptive fields of many photoreceptors include portions of the sky. If the chance of just one short wavelength photoreceptor responding to medium wavelength is negligible, then the chance of two responding in this way is "negligible squared." The chance of all, most, or even a handful of neighboring short-wavelength photoreceptors

Figure 15-4. Individual dorsal root ganglion cells that respond to touch typically have punctate receptive fields (A). For example, the blue cell responds to stimulation of the index finger at any of the blue dot locations illustrated at the left, the red cell responds to stimulation of the red sites and so on. Multiple touch-sensitive primary afferents converge onto one dorsal horn cell (B), which then has a larger, filled-in receptive field (*light gray region*). Within the dorsal column nuclei and thalamus, receptive fields are further modified by both excitatory convergence and lateral inhibition, so that the receptive fields of neurons in the somatosensory cortex (C) are smooth and well delineated (*dark gray area*), and may even be surrounded by a region that elicits an inhibitory response (not illustrated).



Box 15-2

SOUND LOCALIZATION IS FASCINATING BUT OF LITTLE CLINICAL IMPORTANCE.

Central auditory pathways process information about sounds—pitch, loudness, and so on—and also process **sound localization**, meaning the location in space from which a sound originated. Cells, particularly in the superior olfactory complex and the inferior colliculus, fire preferentially when a sound originates from one location over another. This characteristic preference for sound coming from one area constitutes a receptive field.

The neural processing that gives rise to sound localization, an important function for predatory animals like owls and cats, is fascinating. Yet, the chances of an individual's seeking medical care because of a deficit in sound localization are exceedingly small. Therefore, sound localization will not be discussed in this book. Interested readers are referred to the reviews listed at the end of this chapter (Cohen and Knudsen 1999, Konishi 2003).

being excited by medium-wavelength light is essentially zero. Since virtually all of the input to the brain suggests that the sky region consists of short-wavelength light, any lone dissenting input suggesting that the sky emits medium-wavelength light is ignored by the brain. Thus, we reliably perceive a cloud-free sky on a sunny day as a solid blue.

THE BRAIN USES A COMBINATORIAL STRATEGY TO INTERPRET INPUT FROM SENSORY AFFERENTS

The finite number of receptor types yields a finite number of stimulus types represented by sensory afferents to the nervous system. In contrast, the world contains a continuum of stimuli with an infinite number of stimulus properties. This raises the paradox of how a restricted number of receptor types can represent a continuum of stimulus characteristics. In essence, the strategy used by the brain is to combine input from multiple receptor types. For example, we perceive a continuous spectrum of color despite having only three photoreceptor types that support color vision (see Chapter 16). Scenes that reliably stimulate only short-wavelength photoreceptors are interpreted as violet, whereas objects that stimulate both short- and medium-wavelength photoreceptors are viewed as aqua. By using a fine combinatorial code, we can distinguish a range of colors, sounds, and textures using a limited number of sensory afferent types.

SENSORY RECEPTORS TRANSDUCE STIMULUS ENERGY INTO A CHANGE IN MEMBRANE POTENTIAL

Transduction produces a local change in membrane potential called a **generator** or **receptor potential**. By changing the membrane potential of a neuroepithelial cell, a generator potential alters the amount of neurotransmitter released. For example, the membrane potential of a photoreceptor in the dark is about -40 mV. At such a depolarized level, the photoreceptor releases neurotransmitter at a steady rate. When a light flashes, photoreceptors hyperpolarize and consequently release less neurotransmitter. To consider a more typical example, a hair cell in the cochlea has a membrane potential of about -50 mV in the absence of sound. Associated with this resting membrane potential is a moderate rate of neurotransmitter release. When stimulated, the hair cell depolarizes which results in more transmitter release. Yet, the hair cell never fires an action potential. In essence, this means that the hair cell, like other neuroepithelial sensory cells, communicates to a primary afferent by releasing more or less neurotransmitter.

The next cell in line from a neuroepithelial sensory cell, a primary afferent neuron, responds to the amount of transmitter released from the transducing cell by changing the rate of action potential discharge.

Some somatosensory afferents, such as Pacinian corpuscle afferents, possess the transduction machinery at their own peripheral terminals. In these cases, stimulation evokes a generator potential *within* the afferent terminal. If the generator potential is large enough, it triggers an action potential in the afferent. The action potential initiation site is typically just proximal to the terminal. For example, when vibration excites a Pacinian corpuscle, a depolarization occurs in the terminal, the site of mechanical transduction that is covered by a corpuscle. Just proximal (towards the CNS and away from the periphery) to the corpuscle, a sufficiently large generator potential triggers an action potential, which then travels through the Pacinian corpuscle afferent to enter the axon traveling up the dorsal columns of the spinal cord.

THE NUMBER OF SENSORY MODALITIES GREATLY EXCEEDS FIVE

Box 15-3

CODING IS THE WAY THAT MEANING IS REPRESENTED IN THE BRAIN.

The term *coding* in neurophysiology refers to the way in which different neural responses relate to stimuli of varying characteristics. If a dim light and a bright light both elicit the same response from a cell, that cell cannot inform us as to the intensity of the light stimulus. In contrast, if a bright light causes a much larger response than does a dim light, then the cell's response *codes* for light intensity. Although sensory pathways code for information in the world around us, coding is not limited to sensory pathways. For example, neurons in motor pathways code for intended movements.

The popular notion of five senses—sight, hearing, touch, smell, and taste—greatly underestimates the number of modalities, or stimulus types, sensed by humans and other mammals. The vestibular apparatus allows us to sense our head movement and position in space. Proprioceptive afferents sense joint angle and muscle length. Afferents carrying information about pain, innocuous warming, and innocuous cooling are distinct from other somatosensory afferents that code (see Box 15-3) for touch, hair-bending, vibration, and so on. **Interoreceptors**, sensory receptors that innervate viscera, such as the bladder, colon, stomach, and lung, are excited by a variety of internal stimuli such as organ distension or by the products of cell lysis. Under most conditions, interoreceptors function to maintain homeostasis but can, in unfortunate conditions, also alert an individual to potential harm by signaling pain. Each modality has numerous distinct qualities which are coded for by distinct types of afferents. For example, touch can consist of light touch, pressure, vibration, or hair bending. There are four different types of photoreceptors, each with slightly different preferred wavelengths and five different types of taste buds that preferentially respond to salty, sweet, **umami**, meaning savory (see Box 15-4), sour, or bitter substances.

The question of what constitutes a modality is a judgment call. Some might consider all of taste as a modality or all of somatosensation as a modality, although most consider each taste—salty, sweet, umami, and so on—or each cutaneous percept—light touch, pressure, vibration, and so on—as a modality. The latter approach has the advantage that it reflects the critical importance of distinct afferent types to distinct percepts. Yet, one must be careful of the misleading conclusion that one afferent type equals one perception. In reality, activation of multiple afferent types contributes to normal perception, so that the loss of any one afferent type leads to abnormal or weird perceptions. One example of this is color blindness.

Box 15-4

UMAMI REFERS TO THE SAVORY TASTE OF AMINO ACIDS SUCH AS GLUTAMATE.

Glutamate elicits a savory taste perception distinct from the other taste percepts of salty, sweet, sour, or bitter. Glutamate is a major ingredient in meat. The savoriness of umami probably serves an evolutionarily adaptive function to increase the palatability and reward associated with nutritious, protein-rich meat. **Monosodium glutamate**, used as a seasoning, activates umami-preferring taste cells and lends an added savory flavor to food.

Another example is the **paresthesia**, meaning abnormal sensation or sensation that does not match the stimulus, that can accompany certain *neuropathies* that impair the function of one or a few types of somatosensory afferents (see Chapter 18).

ADAPTATION ENABLES PRIMARY AFFERENTS TO CODE FOR A LARGE RANGE OF STIMULUS INTENSITIES

We are able to sense an enormous range of stimuli within each modality. We can hear a whisper, crashing cymbals, and a jet takeoff. We can see the glow of an animal's eyes in the dark, a candlelit meal, and a sun-scorched desert landscape. We can feel the difference between glossy and matte paper, lose sleep over a pea in our bed, and feel the scratch of sandpaper. In most sensory systems, mechanisms of adaptation shift the range of sensitivity. Even with the shift in sensitivity afforded by adaptation, our sensitivity to changes in stimuli is proportional to the level of stimulation. For example, in a dimly lit lecture hall, we easily follow the light from a laser pointer but are unable to see that same light shone on the sidewalk on a sunny day. Likewise, we can feel the weight of a quarter if that is all we are holding but could only detect a role of quarters if we are holding a textbook (Fig. 15-5). In other words our ability to detect stimuli is proportional to the background level of stimulation (see Box 15-5).

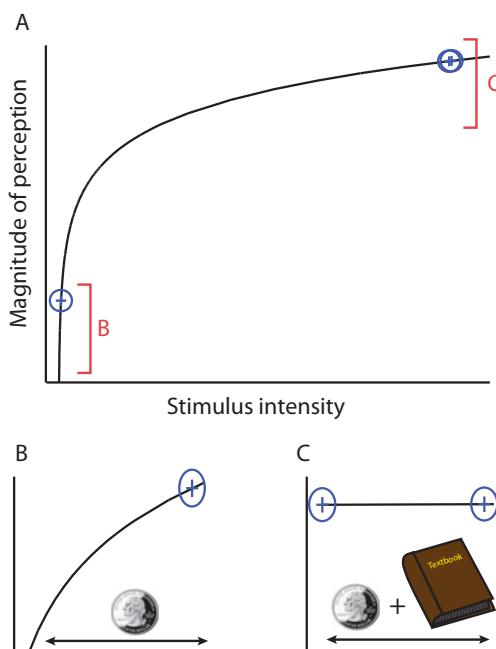


Figure 15-5. A generalized version of Weber's law is graphed in A. Perceptual magnitude is logarithmically related to stimulus intensity. The blue circle at the left, labeled B, shows the predicted perceptual outcome of holding a quarter alone. The two blue circles at the right, labeled C, show the predicted perceptual magnitude of holding a book alone or holding a book with a quarter on top. As illustrated in B and C, the change in perceptual magnitude elicited by a quarter alone is far, far more than the negligible change in perceptual magnitude elicited when a quarter is placed on top of a textbook. In fact, a quarter placed on a book is unlikely to be perceived at all.

SENSORY TRANSMISSION TRAVELS A STEREOTYPICAL ROUTE

Specialized cells use specific molecules to accomplish transduction. In many cases, neuroepithelial cells carry out transduction but in other cases, neurons do. Beyond this one wrinkle, the path from transduction to perception is somewhat stereotyped (Fig. 15-6). After a stimulus is transduced, information about the stimulus is conveyed toward cortex. After the sensory receptor, the transducing cell, to primary afferent synapse,

Box 15-5

WEBER'S LAW TELLS US THAT THE MAGNITUDE OF A DETECTABLE STIMULUS IS A FIXED PROPORTION OF THE BACKGROUND LEVEL OF STIMULATION.

Weber's law relates stimulus intensity to perception. A low-intensity stimulus is perceived on a background of little to no stimulation but not on a background of strong stimulation (Fig. 15-5). For most stimulus modalities, Weber's law holds in the following form:

$$\Delta P = k * \ln(\Delta S / S_0)$$

where ΔP is the change in perceptual magnitude, k is a constant, ΔS is the change in stimulus intensity, and S_0 is the background stimulus intensity. Weber's law tells us that a change in stimulus intensity is only perceived, meaning that $\Delta P \neq 0$, when that change is a large proportion of the background stimulation level. As a simple example of this principle, we see the glow of a candle far more easily in the dark than in sunshine. We feel the weight of a quarter when the coin is the only object in our hand but do not feel the added weight of a quarter while holding a textbook (Fig. 15-5).

the transmission of sensory information includes a minimum of three synapses. The minimum of three synapses includes:

- Primary afferent to secondary sensory neuron
- Secondary sensory neuron to thalamic neuron
- Thalamic neuron to cortical neuron

The primary afferent, which either receives information from a transduction cell or performs transduction itself, synapses onto a secondary sensory neuron. The secondary sensory neuron itself or a neuron that receives input from the secondary sensory neuron projects to the thalamus. Thalamocortical projection neurons then project to sensory cortex. This basic pathway from primary afferent to secondary sensory neuron to thalamus to sensory cortex holds for color vision (see Box 15-6) and somatosensation. Additional intervening neurons are present between the secondary sensory neuron and thalamus in pathways underlying night vision (not illustrated) and audition.

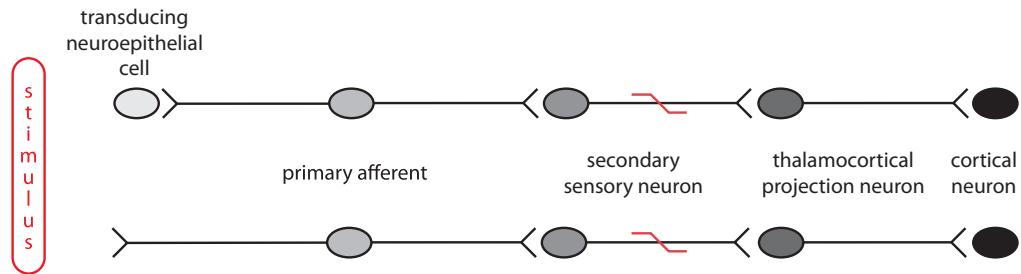
SENSORY PATHWAYS TRANSMIT INFORMATION ABOUT LOCATION, TIMING, INTENSITY, AND TYPE OF STIMULUS

Sensory transmission conveys enough information about a stimulus that we can describe that stimulus in time and space. The following are components of sensory discrimination:

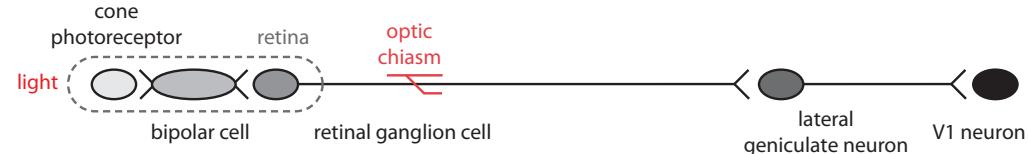
- Stimulus modality
- Stimulus location
- Time of stimulus: onset and offset
- Intensity of stimulus

A common feature used by sensory systems to signal sensory modality is the so-called **labeled line** or lemniscal pathway. Labeled line pathways rely on neurons that receive input from one type of afferent passing that information on exclusively to one set of neurons (Fig. 15-7). In this way, neurons in the central nervous system are activated whenever one type of afferent is active but not when other afferent types are activated. In an idealized labeled line pathway, dorsal root ganglion cells that respond to touch would terminate on a set of dorsal horn cells that only receives input from afferents that signal touch. These dorsal horn cells would in turn excite a group of thalamic neurons that receive only touch-related input and so on, up to somatosensory cortex. In this way, activity in a somatosensory

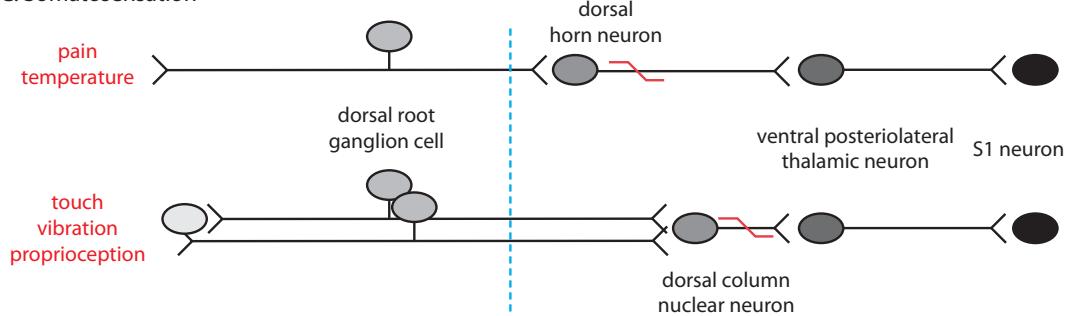
A. Canonical sensory pathway



B. Color vision



C. Somatosensation



D. Audition

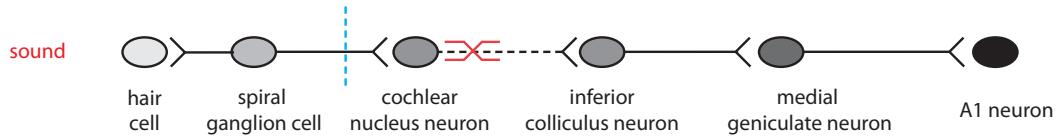


Figure 15-6. **A:** Sensory pathways include a primary afferent, a secondary sensory neuron, and a thalamocortical projection neuron that terminates in sensory cortex. Transduction is accomplished either by a neuroepithelial cell (**top**) or by a primary afferent (**lower**). Typically, the secondary sensory neuron crosses the midline (**red step symbol**), so that inputs from one side reach the contralateral thalamus and cortex. **B:** Light is transduced by photoreceptors in the retina, which in turn synapse on retinal bipolar cells. Bipolar cells receiving input from cone photoreceptors, critical to form and color vision, synapse directly on a retinal ganglion cell. Information from rod photoreceptors, important for night vision, travels through several more synapses to reach the retinal ganglion cell (not illustrated). Retinal ganglion cells project out of the retina (**dashed oval**) to the lateral geniculate nucleus in the thalamus. Nasal retinal ganglion cell axons cross at the optic chiasm (**red step**), whereas temporal ganglion cell axons project ipsilaterally (**red line**). From the thalamus, a thalamocortical neuron projects to visual cortex (**V1 neuron**). **C:** In the case of somatosensation from the body, the primary afferent neuron is a dorsal root ganglion cell, the thalamic neuron is in the ventral posterolateral nucleus, and the cortical neuron is in somatosensory cortex (**S1 neuron**). Somatosensory transduction is either accomplished by the primary afferent itself or by a neuroepithelial cell. For pain and temperature, the secondary sensory neuron is a spinothalamic tract neuron in the dorsal horn, which crosses the midline (**red step**) in the spinal cord. For light touch, vibration, and proprioception, the secondary sensory neuron is a dorsal column nuclear neuron that crosses the midline in the medulla (**red step**) and projects to the thalamus through the medial lemniscus. **D:** Sound is transduced by cochlear hair cells, which contact primary afferent neurons in the spiral ganglion. Spiral ganglion cells synapse in the cochlear nucleus, which in turn project bilaterally (**red steps**) either directly or indirectly (**dashed line**), via the superior olivary complex, to the inferior colliculus. Inferior colliculus neurons project to the medial geniculate nucleus in the thalamus. From the thalamus, a thalamocortical neuron projects to auditory cortex (**A1**). In all panels, the blue dashed line shows the division between the peripheral (**left**) and central (**right**) nervous systems. Note that the visual system is entirely central since the retina is derived from the diencephalic vesicle (see Chapter 3).

Box 15-6

IS THE PHOTORECEPTOR A NEURON OR A NEUROEPITHELIAL CELL?

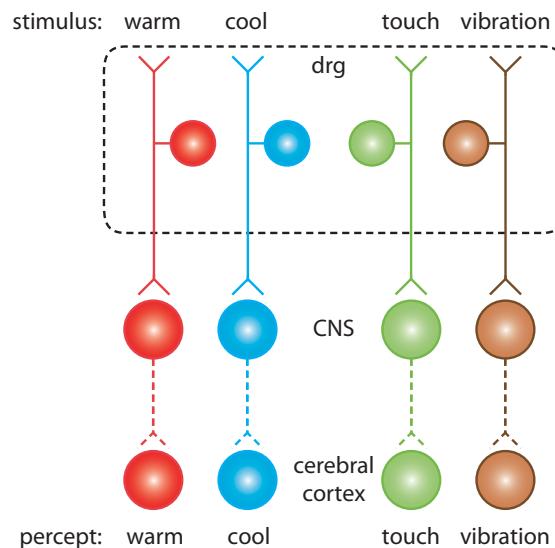
Color vision follows the canonical perceptual pathway if the **cone** photoreceptor, the photoreceptor important in color vision, is considered to be a neuroepithelial cell. In fact, the photoreceptor has characteristics of both neurons and neuroepithelial cells. Photoreceptors are postmitotic cells derived from neuroectoderm, neuronal characteristics. However, like neuroepithelial cells, photoreceptors do not fire action potentials nor do they possess a dendrite or an axon. Moreover, photoreceptors come in a few varieties but are not as individually distinct as most neurons, another way in which they resemble neuroepithelial cells (see Chapter 2).

cortex neuron receiving touch-related input from thalamus would always signal touch. Broadly speaking, all sensation depends on restricted connections: taste input leads to a taste perception and not to a visual perception. Yet, the concept of labeled line pathways is not strictly adhered to as multiple types of afferents within each system—somatosensory, auditory, or visual—interact at all levels of transmission. Thus, for example, a touch stimulus simultaneously activates receptors sensitive to vibration, hair-bending, and mechanical deformation with a variety of characteristics.

Just as modality is conveyed by the identity and connectivity of a neuron, stimulus location is also conveyed by neuronal identity and connectivity. As introduced in Chapter 13, the brain maps the external world. Neighboring parts of the brain process input from neighboring parts of the sensory world. For example, retinotopy refers to an arrangement in which adjacent bits of the retina represent adjacent bits of the visual field. **Tonotopy** refers to the representation of adjacent sound frequencies or tones in adjacent regions of the cochlea or brain (see Chapter 17). In a similar vein, recall that somatotopy refers to the representation of adjacent areas of skin in adjacent regions of the spinal cord or brain. Thus, the theme of mapping, or adjacent representation of continuously distributed sensory “space,” recurs in somatosensation, audition, and vision.

The timing and intensity of a stimulus are coded in the language of action potentials. Because the action potential is finite in duration and cannot occur continuously, the language of the neuron resembles a series of bullets fired from a machine gun rather than the continuous flow of water from a hose. As stimulus intensity increases, the number of action potentials elicited and the frequency of discharge both increase (Fig. 15-8). In addition, the number of *cells* recruited by a stimulus reflects the intensity of that stimulus. At every level of a sensory pathway, far fewer neurons respond to weak stimuli than to strong stimuli.

Figure 15-7. Labeled line or lemniscal pathways are principally responsible for signaling sensory modalities, particularly in the somatosensory and auditory systems. Input from distinct sets of afferents largely stays separate as it travels up the neuraxis. The ultimate result of lemniscal transmission is that perceived modalities reflect afferent modalities to a great degree. Abbreviation: drg, dorsal root ganglion.



THE BRAIN INTEGRATES INFORMATION ABOUT STIMULI FROM MULTIPLE SENSORY SYSTEMS

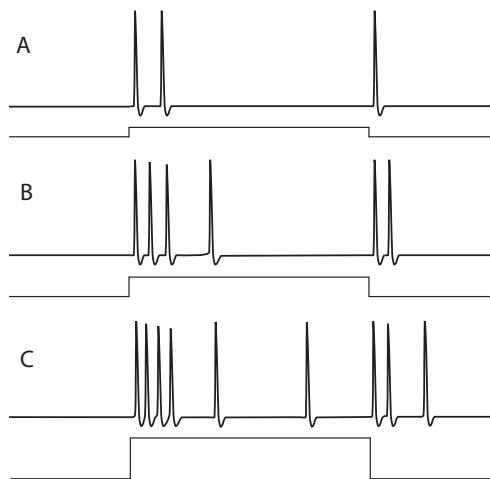


Figure 15-8. The response (top trace in each panel) to a stimulus (bottom trace in each panel) grows as the stimulus intensity (height of the stimulus step) increases. In response to a mild stimulus (A), sensory neurons fire fewer action potentials at lower frequencies than in response to progressively stronger stimuli (B–C). High-frequency bursts of action potentials signal the beginning and end of stimulation. This pattern of response, found in many neurons in sensory pathways, marks the moments of stimulus change, which can be thought of as edges in the time domain. At very strong intensities, the response between the onset and offset begins to fill in (C). An additional mechanism for coding stimulus intensity is the recruitment of more active neurons (not shown).

We refer to the visual, auditory, somatosensory, gustatory, and other sensory systems as though each is a discrete pathway. Yet, the reality is that stimuli in the world stimulate multiple sensory systems. For example, a person has a particular appearance, manner of speaking, and perhaps a consistent smell. As described in Chapter 17, visual clues are critical to understanding speech, even for those of us with normal hearing. Dubbing high-

lights both our ability to ignore mismatches between sensory systems and the problems that can result from such mismatches. When watching a well-dubbed movie in which speech starts and stops as mouth movements start and stop, the clear sound track overrides the visual input that signals words other than those that we hear. In contrast, when a sound track is poorly synchronized to the visual film, we find it very disconcerting when an actor's lips are moving and no words are heard, or when an actor's lips are still while words are heard.

ULTIMATELY, SENSORY PATHWAYS ARE IMPORTANT BECAUSE THEY ALLOW US TO INTERPRET OUR WORLD

The sensory pathways described up to this point are capable of producing a decent description of the world that we see, hear, and feel. However, we do not see visual objects as accurately as a good camera or record sounds as well as a good voice recorder. Discriminating the world pixel by pixel or note by note is not our strength. Instead, we excel at *interpreting* what we see, hear, and feel. As any experienced birdwatcher knows, most birds are identified from a general impression and shape rather than from a laundry list of anatomical features. Similarly, we use the ensemble of clues from multiple senses to identify the person walking down the street, understand a lecture, or ensure that a baby's bottle is warm enough.

The case of Dr. P. described in Chapter 1 dramatically shows us that without the ability to either understand or act upon the meaning of what we sense, the ability to describe stimuli is not particularly valuable or useful.



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CHAPTER 16

SEEING THE WORLD

THE BRAIN RAPIDLY
PROCESSES INPUT TO ARRIVE AT
AN INTERPRETATION OF THE
WHOLE VISUAL SCENE

We and other primates are extremely visual animals. We use our sight for tasks critical to survival such as identification of food, obstacles, family members, and rivals. Sometimes small differences in the visual appearance of objects—think of the difference between a scrumptious mushroom and its evil and poisonous twin—carry great import. At other times, visual details, such as the lines in a sidewalk, are simply distractions that we ignore. Understanding the visual world and its meaning is of great consequence. Half or more of our cerebral cortex participates in vision-related functions, whereas much smaller regions are involved in somatosensation and audition.

The visual system does not act like a camera. Whereas a camera encodes detected light and stores a pixel-by-pixel copy of the visual scene on film, the visual system utilizes parallel circuitry to achieve rapid *comprehension* of a visual scene rather than a detailed recapitulation of the scene. Within the brain, image processing allows rapid detection of abstract features. One way to see this is to look at optical illusions. For example, the image in Figure 16-1A contains no line that describes a star and yet we perceive a star just as we do when a star is actually inked in, as in Figure 16-1B. Illusions such as this demonstrate that our visual system interprets the whole of the visual message, the *gestalt* of the optical image, rather than recording every optical component in view.

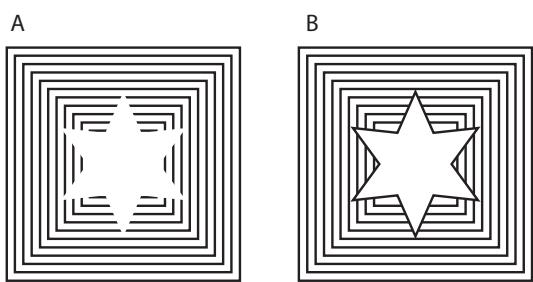


Figure 16-1. Optical illusions reveal that what we see is not a faithful reproduction of what is present in the world. Although there is no star drawn in the image in A, most people readily see a star in A, as well as in B, where a star is actually inked in.

VISUAL PATHWAYS
TRANSFORM POINTS OF LIGHT
AND DARK INTO CONCEPTS

Before starting in on the details of visual processing, it is helpful to review the pathways involved (Fig. 16-2). Light enters the visual system through the eye and is refracted by the **lens** and **cornea**. As a consequence, light from the visual field hits the photoreceptors of the retina. Retinal photoreceptors transduce or transform light into a neural

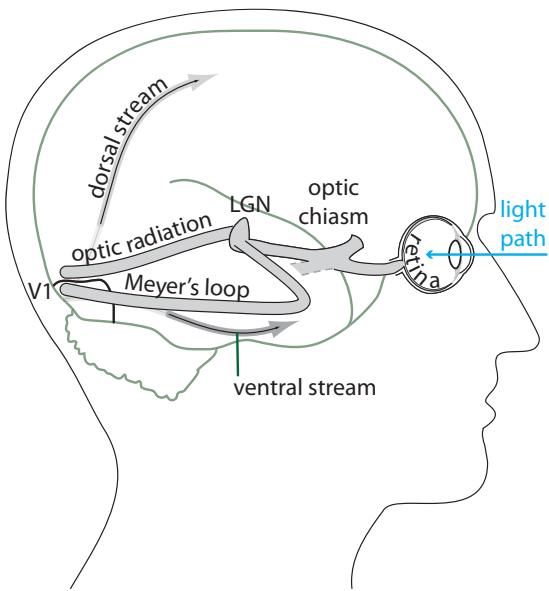


Figure 16-2. When light enters through the eye, it passes through the eye en route to the retina at the back of the globe. In the retina, photoreceptor cells transduce light into electrical energy. Retinal ganglion cells carry information about the visual scene to the lateral geniculate nucleus (LGN) of the thalamus. Lateral geniculate neurons then project to the primary visual cortex (V1). From primary visual cortex, there are two polysynaptic pathways: a dorsal stream, which concerns motion and depth, and a ventral one, which concerns object recognition. Omitted from this diagram are visual pathways involved in circadian rhythm entrainment, orientation movements, eye movements, and pupillary control.

Between the input of photons and the dual outputs of perception and visual guidance, neural circuits transform photons into various visual attributes. Within the retina, the attributes are fairly basic and include features such as:

- Location in retinotopic terms
- Wavelength: short, medium, or long
- Spatial frequency
- Temporal frequency
- **Luminance** changes, meaning changes in the overall brightness (see Box 16-2)

Retinal circuitry accomplishes a high level of image processing that allows the information to be efficiently transmitted to remote locations for image interpretation. Comprehension of the visual scene means understanding the *meaning and relevance* of what we see. Such comprehension requires a large amount of neural territory, with many interconnected circuits. Sufficient territory to support the entirety of visual perception is not available in the retina, a small outpost of the brain. The retina sends processed visual information through the optic nerve and tract to the midbrain and to the lateral geniculate nucleus of the thalamus and thence to primary visual cortex, also termed **striate cortex** or **area 17** (Fig. 16-2).

response, a process termed *phototransduction*. Retinal ganglion cells convey the output of retinal processing through the optic nerve, optic chiasm, and optic tract to the lateral geniculate nucleus. Thalamocortical projection neurons project through the optic radiation to V1 along the banks of the calcarine fissure.

The raw material for all visual processing consists of photons, more photons, and still more photons, all originally derived, directly or indirectly, from the sun's energy. From the totality of photons that impinge on the retina, we perceive objects in place and time, and manipulate or attend to particular objects. In this chapter, we consider how neural processing of optical information transforms incident light into (1) *ideas* about the world and (2) a continuously updated *guide* for our physical interactions with the world.

Our perception of the visual field is not uniform in that we see with the highest **acuity**, or resolution, within the central part, 5 degrees or so, of the visual field. For example, we read type by looking directly at the type, so that light from the type hits the center part of the retina, a region known as the **macula** (see Box 16-1). The very center portion of the macula is marked by a depression in the retina called the **fovea**. The peripheral retina also has its particular advantages. For example, if you want to spot a dim star at night, the best strategy is to fixate just to the side of the expected location of the star. This is because the **peripheral retina**, although not supporting high-acuity vision, is optimal for detection of dimly lit scenes.

Between the input of photons and the dual outputs of perception and visual guidance, neural circuits transform photons into various

visual attributes. Within the retina, the attributes are fairly basic and include features such as:

FIXATION ENSURES THAT THE LIGHT FROM OBJECTS OF PARTICULAR INTEREST IS FOCUSED UPON THE PART OF OUR RETINA THAT SUPPORTS HIGH-ACUITY VISION.

When we look at an object, so that light from that object is focused onto the central part of our retina, we are fixating on that object. Visual fixation is an active process (see Chapter 26). To appreciate the differences in acuity across the visual field, spread your fingers out and hold your hand at arm's length. While staring at your middle finger, compare how much detail you can see on your index and ring fingers with the amount of detail that you see on your pinkie and thumb. The detail that you see on your index and ring fingers is close to that which you see on your middle finger and substantially more than what you see on your pinkie and thumb. To make this point even more clearly, make a small mark, a letter or a number, on each digit, and fixate on your middle finger: You can easily make out the marks on your index and ring fingers but not those on your pinkie and thumbs.

As illustrated by the exercises above, visual acuity falls off rapidly for objects outside of the 5 degrees or so of the visual field that hits the central area of the retina, termed the **area centralis**. The area centralis contains a concentration of **lipofuscin**, a yellow (*lutea* in Latin) pigment, in humans and many other animals. Because of this collection of pigment, the area centralis is also called the **macula lutea** or simply the macula. Near the center of the macula is

a physical indentation or pit in the retina. This pit is termed the **fovea** (fovea is Latin for small pit) and represents a much smaller area than the macula. The fovea receives light from the central degree, $\frac{1}{2}$ a degree around the mid-point of the visual field. To get an idea of how big a degree of visual space is, hold your thumb out at arm's length; the horizontal arc subtended is about 2 degrees. Note that because fixation serves to position the eye so that light from objects of interest hits the fovea, the term **foveate** is sometimes used as a synonym for fixate.

Eye movements such as fixation, **smooth pursuit**, and the **vestibuloocular reflex** keep an area or object of interest focused on the macula, maintaining fixation even as either you or the point of interest moves. Other eye movements, exemplified by ballistic shifts in eye position termed **saccades**, serve to *shift* the point of fixation. Vision is key to eye movements. For example, we cannot accurately track a bird flying through the sky without a visually derived estimate of the bird's location, trajectory and speed. Eye movements are also critical to vision. Without proper yoking of the two eyes' positions, the same visual scene will not hit the foveae of both eyes. Then each eye will "see" a different scene. Recall from Chapter 10 that this condition is known as **diplopia** or double vision.

Output from the retina is carried by retinal ganglion cells. The retina sends out many parallel channels of partially processed optical information with each channel carried by a different class of retinal ganglion cells. Within the thalamus and visual cortex, optical features are combined to tell us more about the visual image. For example, primary visual cortex uses position and time information to determine the orientation of edges. Moreover, both the lateral geniculate nucleus and primary visual cortex not only receive visual information but also receive input about expectation, attention, fatigue, sounds, and so on (see Chapter 13). By combining visual and mental information, we are able to "find Waldo" so to speak, in other words, to *look for* particular objects or particular colors or any other particular visual features. We may also perceive things differently than they actually are (Fig. 16-3). For example, in

THE RETINA PROCESSES LUMINANCE TO DERIVE THE FUNDAMENTAL OPTICAL PROPERTIES OF SPATIAL AND TEMPORAL CONTRAST.

The retina provides the initial processing of luminance changes that occur across space and time. Two concepts are critical to understanding this processing:

- **Spatial contrast** is a measure of how much the luminance, or overall brightness, changes across a unit of space.
- **Temporal contrast** is a measure of how much the luminance changes per unit of time.

We perceive stimuli with temporal and spatial contrast values within certain ranges. We cannot see stimuli with either spatial or temporal contrast that is too low or too high. For example, the changes in brightness across a day occur so slowly, at such a low temporal frequency, that we cannot detect the time of day by the amount of incident light. At the other extreme, we are blind to the flicker of movie projection or computer displays despite the fact that both are refreshed about 50–100 times per second. In between these two extremes, we are very sensitive to the flicker of strobe lights, flashes of lightning, and blinking traffic lights.

Our sensitivity to spatial contrast is entirely analogous to the situation with temporal contrast. In a black-and-white image, an edge is essentially a change in luminance. The greater the contrast, the easier it is to perceive an edge. Yet, we have low contrast sensitivity at very high and very low spatial frequencies (see Fig. 15-3B). The visual world is a blend of components with low to high spatial frequencies (see Fig. 15-2B-D). For example, at the edge of a cloud in a sunny blue sky, incident light changes from white to blue in less than a degree. This edge is a high-frequency component. Yet, the contrast between the body of the white cloud and the blue sky is at a low spatial frequency.

Different activities depend preferentially on different spatial and temporal frequencies. As the reader has likely figured out by now, reading depends on high spatial frequencies. Navigation depends on both low—“go toward the lighted areas”—and high—“don’t hit your head on the tree limb”—spatial frequencies. The detection of movement is largely dependent on low spatial frequencies. All of this is important because, as we shall see, diseases can affect low or high spatial contrast sensitivity preferentially and therefore impact people’s lives in different ways.

Figure 16-3A, the hen on the lower left looks smaller than the hen on the upper right, even though they are exactly the same size (Fig. 16-3B). In this illusion, information about the effect of distance on size misinforms us that the distant hen is larger than the close hen. In fact, even our sense that one hen is closer to us than the other in this flat, two-dimensional image is based on our learned knowledge that opaque objects block the view of more distant objects.

From primary visual cortex, optical features are combined in various ways to allow visual inferences of two basic classes:

- *Perceptions of the world:* What are the objects that we see? Where are they? How are they related to each other?

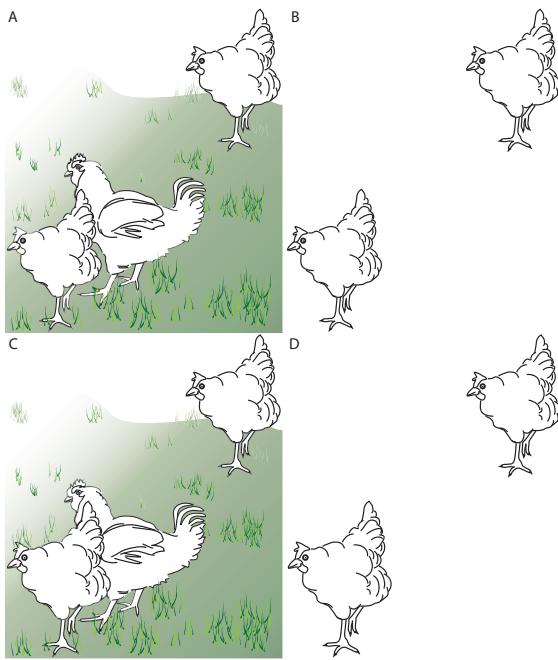


Figure 16-3. A: Despite the two-dimensionality of this image, the hen on the bottom left is perceived as in the foreground, and the one on the upper right is seen as part of the background. This perception results from the hen on the left's blocking out part of the rooster: we have learned that solid objects block light from more distant objects. Because we perceive the hen on the left to occupy the foreground, we also perceive the left hen as smaller than the hen in the upper right. However, as shown in B, the two hens are exactly the same size. We perceive the foreground hen as smaller because we know that objects in the foreground make larger retinal images than objects in the background. Therefore, we shrink a near object of the same size as a far object to fit with our expectation that things closer to us are larger than objects that are farther away. This process takes place unconsciously within visual pathways within the cortex. To perceive the hens as the same size within a three-dimensional context (C), the hen in the foreground must be enlarged as shown in D.

- *Guidance for movements:* How can I reach for, avoid, or watch with my eyes an object in the world? To where in visual space should I turn my attention?

Two different cortical pathways support the goals of seeing the world and guiding movements (Fig. 16-2).

- The dorsal visual stream, often referred to as the “where” stream, carries visual information that directs attention and movements to particular *locations*. This pathway occupies much of parietal cortex. These areas are responsible for guiding one’s own movements and for understanding the goals and outcomes of others’ movements.
- Recognizing visual objects and the structure of the visible world is dependent on the ventral visual stream, which occupies large parts of temporal cortex and is often referred to as the “what, who” stream. The inferotemporal cortex is critical to recognizing what the points of light and darkness represent, understanding the gestalt from the details. Within the inferotemporal cortex lies the **fusiform face area** which, as will be described further below, is critical to our recognition of individual faces.

Nonvisual information related to movements we are making, expectations, previous experiences, recent history, and sensory inputs from touch, sound, taste, smell, and so on influences what we think we see and what we do with what we see. For example, correctly reporting the ink color that spells the name of a different color is more difficult than reading the name of that color written in either black or in the congruent color (Fig. 16-4). The difficulty in verbalizing the color of the ink does not stem from any *optical problem* but rather from the perceived incongruity between letters and color. The color word task, called

A	black	green	orange	blue	brown	red	violet
B	xxxxxx	xxxxx	xxxx	xxx	xxxxxx	xxxxx	
C	violet	brown	black	blue	red	orange	green

Figure 16-4. The Stroop test shows how influential expectation can be upon visual tasks. A: Read aloud each word. Next name the color that each word is written in. Both of these tasks are straightforward and easily accomplished without delay. B: Name the color that each group of “X”’s is written in. As in A, this is an easy task as there is no conflict. C: Read aloud each word and then name the color that each word is written in. Both of these tasks are difficult, the latter one even more so than the former. The tasks are usually accomplished after only a delay. The task of reading colored letters is not difficult when those letters spell the congruent color (A). Similarly, the task of naming the color of letters is not difficult when those letters either do not spell an incongruent color (A) or do not form a word (B). Thus, the delay in these tasks is due to resolving the conflict between form—the spelled word—and color. This delay is termed the Stroop effect.

the **Stroop task**, also highlights the importance of attention. Vision is not passive. If you remember nothing else, remember that vision is context-specific. We see what we pay attention to and in some instances what we want to see. *The attention that we pay to a visual scene can be as critical to our comprehension of that scene as are the points of light and dark.*

Visual perception is only one end point for information coming into the eyes. Additional functions that use input from the eye but either always operate without conscious visual perception or *can* operate without conscious awareness include:

- The entrainment of the circadian rhythm to light and dark cycles
- Regulation of pupillary size
- Orienting movements that change the direction of gaze by turning the eyes and head and/or looking farther away or closer
- Eye movements, such as smooth pursuit

Only the first two topics will be touched upon in this chapter. The latter two topics are discussed in Chapter 26.

In a final section, we discuss the importance of normal development to high-acuity vision. When the visual experience of a baby or infant is disrupted during the **critical period**, the first few years of life in humans, vision does not develop normally, and adult vision is irreversibly compromised.

EYE LENGTH, THE CORNEA, AND THE LENS COMBINE TO FOCUS LIGHT ON TO THE RETINA

The eye acts like a camera, gathering light reflected off objects throughout the visual field and creating, as does a camera, a reversed image on the retina (Fig. 16-5B). Three anatomical features are critical to the eye's ability to focus light onto the retina:

- The length of the eye
- The cornea
- The lens

The cornea and the lens combine to refract light, with the cornea producing about two-thirds of the total refractive power of the eye. The length of the eye, from cornea to retina, must be exactly matched to the angle of **refraction** in order for light to be focused on the retina (see Box 16-3).

As shown in Figure 16-5A, the cornea bulges out from the eye, forming a spherical surface that refracts incident light (see Box 16-3) toward the **optical axis**, a line running from center of the pupil to the center of the retina. In this way, *the cornea does the bulk of the focusing achieved by the eye*. Using the cornea alone, we would

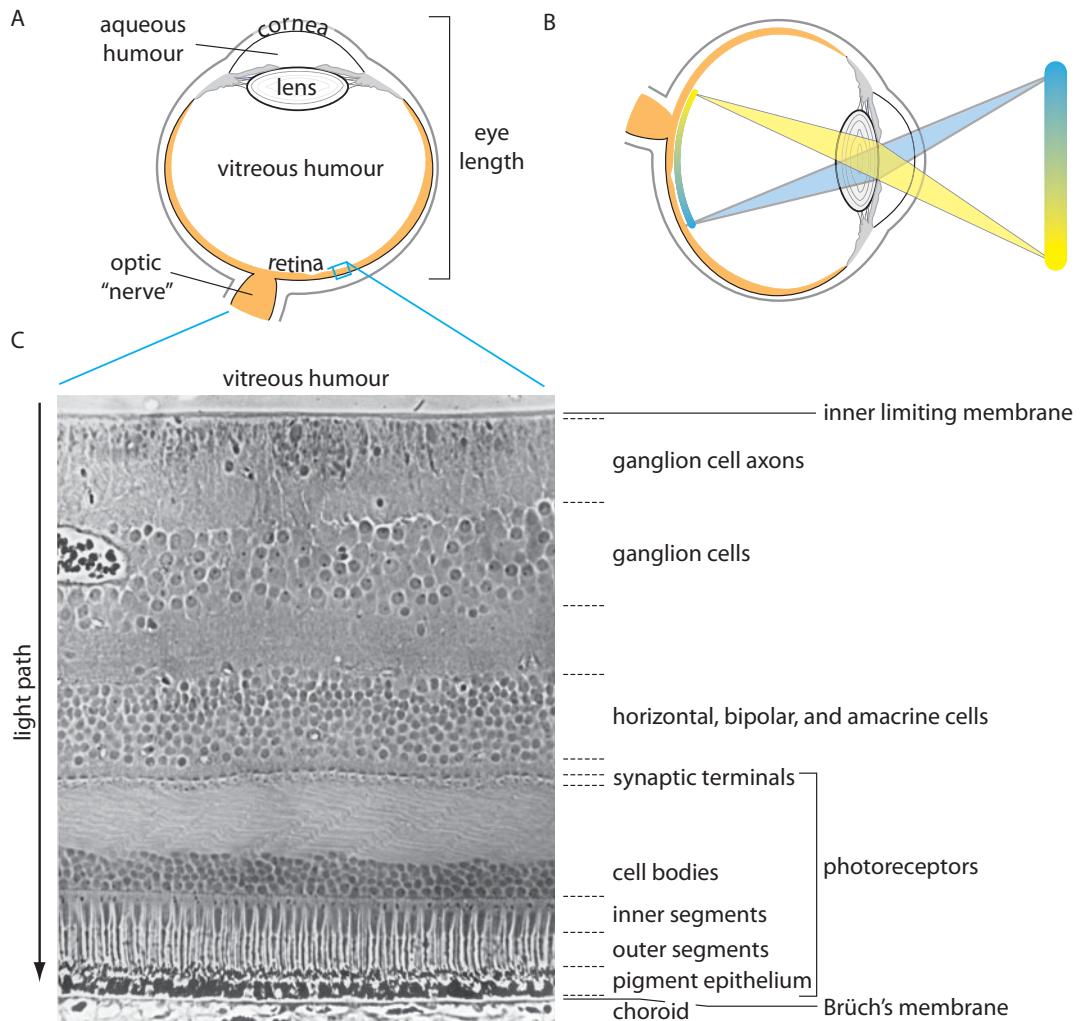


Figure 16-5. A: This cartoon shows a horizontal cross-section through the right eye as viewed from above. To reach the neural retina, light must pass through the transparent parts of the eye. Incident light bends upon encountering each interface: air to tears, tears to cornea, cornea to aqueous humor, aqueous humor to lens, lens to vitreous humor, and finally vitreous humor to retina. Yet, the largest changes in refractive index occur at the cornea and at the lens, and consequently, light bends principally at these two interfaces. The output of the retina travels through the optic nerve. B: The cornea and lens effectively focus the cone of light arriving from any one spot in the visual field onto one spot on the retina. All images on the retina are reversed in both the horizontal (shown, this eye is simply rotated 90 degrees clockwise from its orientation in A) and vertical (not shown) planes with respect to the source within the visual field. C: A cross-section through the human retina shows a laminated structure. Incident light arriving from the vitreous humor passes through a layer of ganglion cells and a second layer of retinal cells (a mixture of horizontal, bipolar and amacrine cells) before reaching the photoreceptors. Photoreceptors are oriented with synaptic terminals closer to the vitreous humor and outer segments, where phototransduction takes place next to the pigment epithelium.

Photograph in C reprinted from Boycott B.B. and Dowling J.E. Organization of the primate retina: Light microscopy. *Phil Trans R Soc B* 255:109–84, 1969, with permission of the publisher, The Royal Society.

still see forms in the world but those forms would be blurry and not in fine focus (see Boxes 16-4 and 16-5).

Light travels from the cornea through the **aqueous humor** (Fig. 16-5A). Since the refractive indices of the cornea and the aqueous humor are very close in value, no appreciable refraction occurs at this stage of the light path. However, when light hits the lens, with a higher refractive index, light is bent further toward the optical axis. The additional refraction produced by the lens provides a fine focus, rendering forms sharp and crisp rather than blurry—at least ideally.

Box 16-3

LIGHT BENDS AND REFLECTS WHEN IT HITS THE INTERFACE BETWEEN TWO DIFFERENT SUBSTANCES.

As you recall from basic physics, when light, traveling as a wave in a straight line, crosses the interface between two different media, the light path changes in several ways:

- Some light intensity is lost as a portion of the incident light is reflected.
- Light **refracts** or bends upon encountering an interface with a change in **refractive index**, a measure of the degree to which light slows down relative to its speed in a theoretical vacuum, given as 1.0. The refractive index of air is only a few millionths more than the refractive index of a vacuum; we ignore this minuscule difference. Water has a refractive index of 1.33, meaning that light slows to 75% ($=1/1.33$) of the “speed of light” when traveling in water. The cornea’s refractive index is very close to that of water, whereas the lens’ refractive index is close to that of glass, about 1.42. There is one exception to the rule of refraction at an interface with a change in refractive index: light that hits an interface *perpendicularly*, does not bend and yet still slows.
- Light of different wavelengths refracts at slightly different angles, producing **chromatic aberration**.

This is illustrated in Figure 16-6. Incident white light carries a range of wavelengths, including wavelengths normally perceived as violet, yellow, and red. As mixed wavelength light passes through the cornea and subsequently the lens, long wavelength light (red) is bent less than short wavelength light (violet, blue), resulting in an image of mixed wavelengths being focused to a variety of distances (Fig. 16-6A-B). In the case of the human eye, light of a wavelength commonly perceived as yellow is focused to the site of phototransduction, whereas longer wavelength light focuses to a more distant plane and shorter wavelength light to a nearer plane. To put short wavelength light into focus, we relax accommodation, looking farther away, and we accommodate in order to put long wavelength light into focus. As we practice this all the time, we learn that red objects require accommodation and blue objects require a relaxation of accommodation. The result of this is that we perceive blue objects to be farther away than red objects located at the same distance (Fig. 16-6C-D).

Box 16-4

LENS OPACITIES OR CATARACTS ARE THE LEADING CAUSE OF BLINDNESS IN MANY COUNTRIES.

Cataracts are opacities of the lens which impair vision and can ultimately cause total blindness. There are a large number of reasons why cataracts arise. Some are congenital and many develop as we age. In Western countries, surgeries to remove the lens from the lens capsule and place a clear implant within the capsule are both available and successful in the vast majority of cases. Unfortunately, surgery is far less available in developing countries.

Consequently, in developing countries, cataracts are often the leading cause of **blindness** both in older individuals who develop cataracts as they age and in children born with congenital cataracts. Adding to the urgency of this situation, for those born with congenital cataracts, surgery during adulthood is useless as developmental and irreversible harm to visual acuity has already occurred (more on this below).

Box 16-5

ASTIGMATISMS RESULT FROM CORNEAL ABNORMALITIES.

The corneal surface should curve spherically in all directions. However, sometimes, the cornea is more cylindrical in that the radius of curvature is not uniform across all orientations, a condition known as **astigmatism**. As a result, lines in one orientation may be distorted or blurred. Most astigmatisms can be corrected with appropriate lenses.

ACCOMMODATION ALLOWS FOR FOCUS ON NEAR OBJECTS

The cornea, like a lens in eyeglasses, is fixed in shape. In contrast, the shape of the lens can be changed, with the result that the focal point of the eye can change (Fig. 16-7A). When the lens shape is more spherical, near objects are in fine focus. This adjustment of the lens is known as **accommodation** and is one element of the near-focusing triad, with pupillary constriction (see Box 16-6) and convergence of the two eyes comprising the other two components (see Box 10-4). Unfortunately, all of us lose the ability to accommodate if we live for at least five decades (see Box 16-7).

At rest, the human eye is built for distance viewing. The lens is flattened as it is held taut by **zonule fibers** that stretch from the lens capsule posteriorly and laterally to the *relaxed* ciliary muscles (Fig. 16-7). Upon voluntarily shifting the depth of focus from far to near, lens accommodation automatically accompanies convergence of the eyes and pupillary constriction. For example, as you shift your

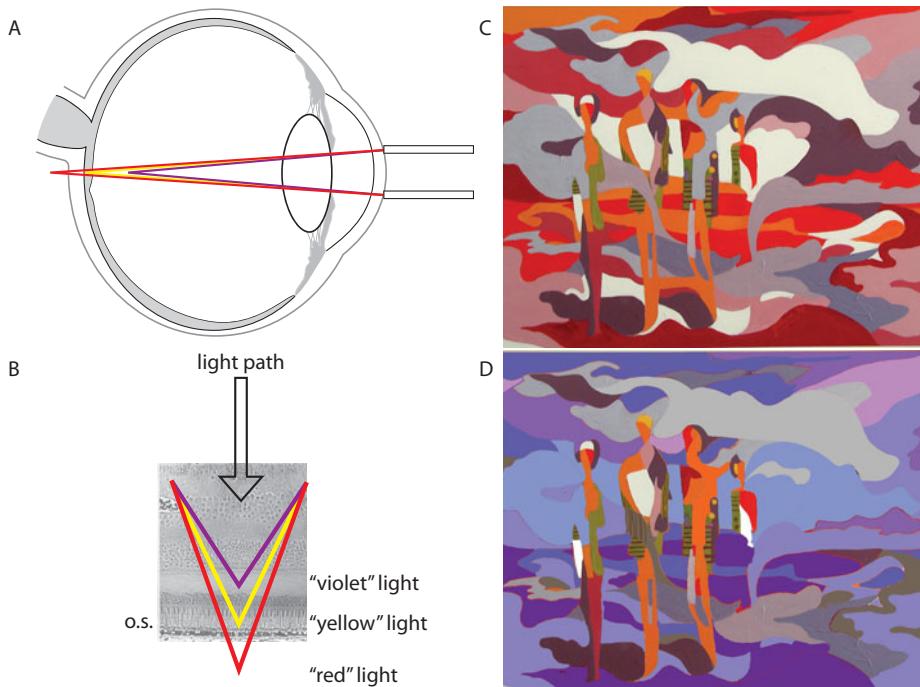
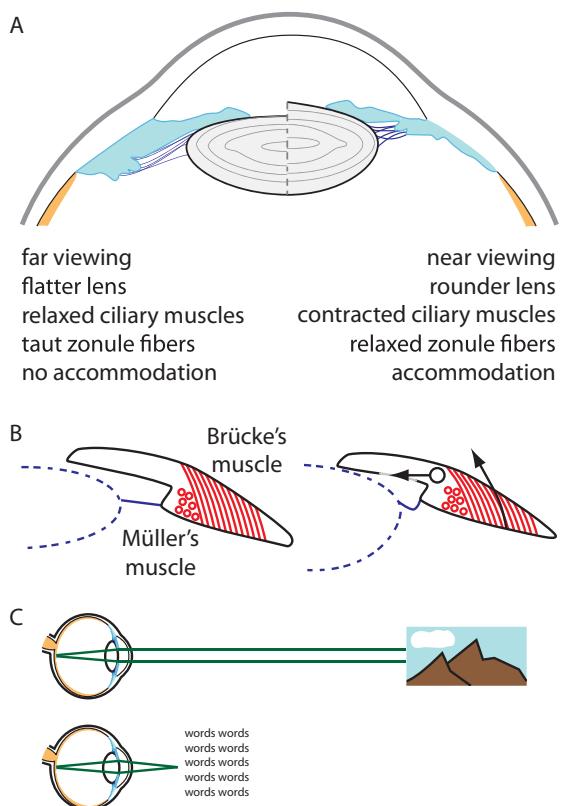


Figure 16-6. A-B: Incident white light (black outlined rectangles) carries a range of wavelengths, including wavelengths normally perceived as violet, yellow, and red light. As white light passes through the cornea and subsequently the lens, long wavelength light (red) is bent less than short wavelength light (violet, blue), resulting in an image of mixed wavelengths being focused to a variety of distances. In the case of the human eye, light of medium wavelength, commonly perceived as yellow, is focused to the level of the photoreceptor outer segments (o.s.), whereas longer wavelength light focuses to a more distant plane and shorter wavelength light to a nearer plane. Thus, to put long wavelength light into focus we accommodate, as though we were focusing on something near. As we practice this all the time, we learn that long wavelength objects require accommodation and short wavelength objects require a relaxation of accommodation. The result of this is that we perceive short wavelengths to be farther away than long wavelengths located at the same distance. C-D: Artists use the perceptual trick resulting from chromatic aberration to either lend a perception of depth (D) or to flatten an image (C). Warm colors—red and orange—are perceived as in the foreground, whereas cool colors—blue and violet—create a perception of depth.

Photograph in B reprinted from Boycott B.B. and Dowling J.E. Organization of the primate retina: Light microscopy. *Phil Trans R Soc B* 255:109–84, 1969, with permission of the publisher, The Royal Society. Paintings in C and D kindly provided by Jane S. Mason.

Figure 16-7. A rounding up of the lens, accommodation, changes the refraction for light hitting the lens, biasing the eye's fine focus to near objects. **A:** During far viewing (left), there is no accommodation, and the ciliary muscles are relaxed. Zonule fibers are taut when the ciliary muscles are relaxed. The taut zonule fibers pull on the lens, rendering it flattish. For near viewing (right), accommodation is accomplished by contraction of the ciliary muscles, which moves the **ciliary body** anteriorly and medially. As a result, the zonule fibers relax and this allows the lens to adopt its more round, relaxed shape. **B:** There are two sets of ciliary muscles critical to changing lens shape. Müller's muscles are circumferential fibers that are located medially; when they contract, the ciliary body moves medially and forward. Brücke's muscles are radially oriented, like the spokes on a wheel, and pull the ciliary body forward and medially when they contract. Contraction of both types of ciliary muscles moves the ciliary body closer to the lens and thus allows the zonule fibers to relax, which in turn allows the lens to ball up. **C:** When looking at mountains, or anywhere at optical infinity, incident light arrives along nearly parallel paths. In contrast, during near viewing, incident light arrives along convergent angles. The changes in lens shape, zonule fiber length, and so on that are illustrated here are hugely exaggerated as the difference is barely perceptible even when exaggerated many fold.



focus from the teacher at the front of a lecture hall to your notebook, the near triad, including accommodation, occurs.

Recall from Chapter 12 that preganglionic parasympathetic neurons in the Edinger-Westphal nucleus carry the accommodative signal to the ciliary ganglion. Accommodation is then accomplished when ganglionic neurons fire, leading to the contraction of the ciliary muscles. Contraction of the circumferential **Müller's muscles** brings the ciliary body forward and medial, which in turn relaxes the zonule fibers (Fig. 16-7B). A second ciliary muscle, **Brücke's muscle**, radiates out from the

Box 16-6

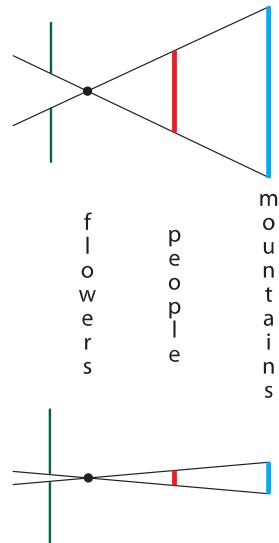
PUPILLARY CONSTRICION PRIMARILY SERVES TO INCREASE THE DEPTH OF FOCUS.

Pupillary constriction accomplishes several purposes. A dilated pupil admits more light than does a constricted pupil, but only by a factor of two or so. Pupillary diameter can also signal highly charged emotions, widening during fright or extreme pain. Yet, the effect of pupillary diameter on depth of focus and image fidelity is arguably the most important function. Just like a pin-hole camera, a narrow

pupil prevents blur from objects at a range of depths (Fig. 16-8). A narrow pupil also limits the number of optical aberrations and consequently the amount of image distortion. Pupillary constriction is thus a critical part of the near triad, which along with lens accommodation and eye convergence, occurs automatically when we fixate on near objects.



A1. wide aperture/pupil



B1. narrow aperture/pupil



Figure 16-8. Two photographic images, one obtained through a pinhole aperture (B), show the effect of a narrow camera aperture, or pupil, on depth of field. **A:** When the aperture of a camera is open, focus is restricted to a narrow depth of field. Only the foreground flowers are in focus. The people in the street and the clouds and mountains in the far distance are all blurry. **A1:** A wide aperture allows a circle of blur from other depths to enter. **B:** Narrowing the aperture of a camera, like constricting the pupil, has a profound effect on depth of field. In this photograph, taken through a pinhole aperture, the flowers, people, mountains, and clouds are in focus. **B1:** Virtually all of the light entering through a narrow aperture arises from a narrow cone of space, resulting in minimal blur at any depth. The result is a large depth of field.

Photographs kindly provided by Claude Perreault.

lens, and its contraction shifts the zonule fiber attachment medially and forward, which also results in shortening the zonule fibers. Relaxing the zonule fibers' tension on the lens capsule allows the lens to ball up, become more spherical. Just as for eyeglass lenses, a lens with a more spherical profile creates greater refraction due to the increased curvature. Thus, lens accommodation brings near objects into focus.

Box 16-7

THE LENS INEVITABLY BECOMES FIXED IN SHAPE BY MIDDLE AGE.

Our lens loses elasticity progressively throughout life. In our fifth decade, this loss reaches a point at which the ability to accommodate is severely compromised. This is as sure of happening as are death and taxes. As we age, it takes longer and longer to change our lens shape by less and less. For most of us, this ultimately requires us to hold reading material farther and farther away from our eyes in order

to focus on the letters. When holding pages at arms' length no longer suffices, "reading glasses" become absolutely necessary for near vision. The inability to focus on near objects is termed **presbyopia** (ancient Greek for *old man-eye*). Some myopic individuals escape the need for reading glasses, being able to read without any glasses, even as their lens stiffens and accommodation is lost.

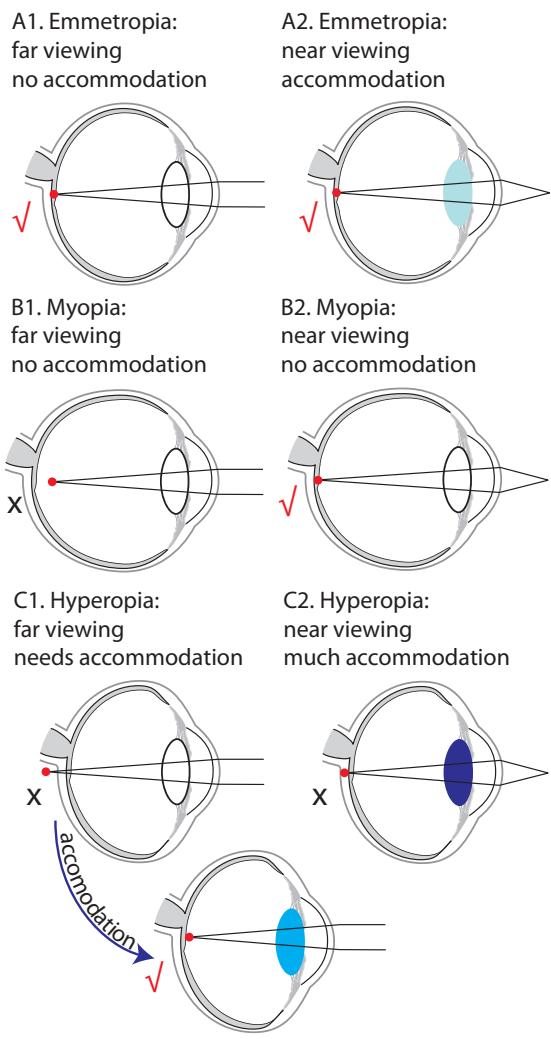


Figure 16-9. Aberrant eye length is the leading cause of refractive vision problems. Ideally, the eye grows to a length that matches the refractive power of the lens and cornea, so that light is focused on the retina without any accommodation (A1). This condition is emmetropia. The increased refraction afforded by accommodation brings near objects into focus in emmetropic people (A1). B: When the eye is too long, far objects come into focus somewhere in the vitreous humor (B1), but near objects come into focus on the retina, even with no or very little accommodation (B2). C: When the eye is too short, far objects come into focus behind the eye (C1). Hyperopic individuals may engage the near triad while looking at far objects and thereby increase the refractive power of their eyes. This can result in far objects coming into focus. However, even with maximal accommodation, near objects cannot be properly focused upon without corrective lenses (C2).

A DEVELOPMENTAL PROGRAM DICTATES EYE GROWTH TO A LENGTH THAT SUPPORTS FOCUS OF DISTANT IMAGES

Ideally, the eye focuses light perfectly onto the outer segments of the photoreceptors where transduction occurs. **Emmetropia** is the ideal condition when the eye, with relaxed ciliary muscles, focuses light from far objects onto the retina (Fig. 16-9A1). Emmetropia depends on the retina's being located at just the right distance from the cornea for the distant visual world, anything past about 25 feet, to arrive in focus when the lens is not accommodated. With accommodation, near objects are focused on the retina of individuals with emmetropic eyes (Fig. 16-9A2).

Any tiny error in the length of the eye, of less than a millimeter, will change the focus, producing a measurable, and luckily correctable, defect in vision. When the length of the eye, from cornea to retina, is too long, far images will be focused at some point within the vitreous humor (Fig. 16-9B1). Yet, the path of light depends not only on the change in refractive index at an interface but also on the angle at which light arrives at the interface. Light arriving from near objects is perfectly focused in people with long eyes, even with little or no accommodation (Fig. 16-9B2). Therefore, individuals with long eyes see near objects in focus and are consequently termed **near-sighted** or **myopic** (see Box 16-8).

In people with short eyes, distant images arrive at the retina out of focus, with the theoretical focal point located somewhere behind the retina (Fig. 16-9C1). This condition is known as **hyperopia** (see Box 16-9). We are, in fact, born hyperopic. As we grow, our eye lengthens to match exactly the refractive power of the eye through a process known as **emmetropization**. The ideal end point of emmetropization is that distant objects are perfectly focused on the retina—in another word, emmetropia. Emmetropization is vision-dependent, in that it depends on the quality of the images focused on the retina. Yet, it occurs independently of the brain. Rather, emmetropization involves *local* interactions between the retina, which somehow detects the blur from out of focus images and the **sclera** (see Box 16-10), the outer limiting membrane of the eye. The most typical consequence of defective emmetropization is myopia, a condition that affects a large proportion of the human population in industrialized nations. In some areas, the majority of people are myopic!

When viewing images at a distance, hyperopic individuals can correct for refractive errors by employing accommodation (Fig. 16-9C1). However, at short distances, accommodation may not be powerful enough to focus near images onto the retina of a short hyperopic eye (Fig. 16-9C2). Therefore, hyperopia is often termed **far-sightedness**. The vast majority of cases of both myopia and hyperopia can be fixed with appropriate corrective lenses.

Box 16-8

MOST NEARSIGHTEDNESS RESULTS FROM FAULTY GROWTH, OVERGROWTH IN FACT, OF THE EYE.

Most cases of myopia are associated with a long eye, resulting from aberrant emmetropization, or development of emmetropia. Emmetropization is powerfully influenced by environmental factors such as how much near- and far-viewing an individual does during infancy, childhood and even during puberty when the eye continues to grow along with the body. During development, the retina not only detects unfocused images but appears to distinguish between images errantly focused in front of the retina (myopic) from those focused behind the retina (hyperopic). This distinction may be accomplished by using cues derived from chromatic aberration. A hyperopic lack of focus produces a GROW signal that is sent to the sclera, whereas a myopic lack of focus STOPS eye growth.

There has been an explosion in the incidence and severity of myopia in South and East Asian countries. This epidemic of myopia is thought to result at least in part from children spending too much time viewing near objects, typically while reading or viewing hand-held game consoles. So much near vision is thought to exert detrimental

effects through several mechanisms. One popular idea is that overtaxing accommodation induces eye growth which thereby lessens the need for so much accommodation. A second possibility is that the paucity of time spent viewing distant objects, as occurs when playing in open spaces, contributes to the increased incidence of myopia. Viewing distant scenes may be necessary to establish a reference point for far vision that can serve as the standard for emmetropization. Finally, convergence is a fast process mediated by ionotropic receptors and fast skeletal muscles, whereas accommodation is slow, mediated by metabotropic receptors and slow smooth muscles. Therefore, there is an *accommodation lag*, after the eyes converge and before the lens changes shape, which may produce image blur that in turn triggers further eye growth, ultimately leading to myopia. Beyond the costs of correcting myopic vision, myopia is a risk factor for a number of serious vision problems such as **retinitis pigmentosa** and **glaucoma**. Therefore, the developmental biology underlying eye growth is not only fascinating but important to understand.

Box 16-9

WHEN SEVERE, HYPEROPIA CAN COMPROMISE THE DEVELOPMENT OF NORMAL VISION.

Despite the common moniker for hyperopia—farsightedness—a short eye does not bring far objects into focus. Yet, a person with short eyes *can* bring far objects into focus simply by converging their eyes and thereby engaging the near triad. For reasons that remain mysterious, some but not all individuals with severely hyperopic eyes develop **accommodative esotropia**. Esotropia means that an eye turns inward, toward the nose. When both eyes are esotropic, this gives the appearance of cross-eyes. Accommodative esotropia is esotropia that

results from early and severe hyperopia. Like any **strabismus** or misalignment of the eyes, accommodative esotropia is dangerous as it can prevent proper development of high acuity vision (see last section of this chapter). Thus, while all babies are hyperopic and may as a result have a somewhat cross-eyed appearance (Fig. 16-10), parents and physicians should be alert to extreme esotropia and the possibility that an infant may develop accommodative esotropia.



Figure 16-10. A 2-month-old infant shows the characteristically slightly cross-eyed look of a newborn. Since an infant's eyes are still growing, newborns are born hyperopic. Eye convergence with the engagement of the near triad (see Chapter 10) helps bring visual objects into focus. Photograph kindly provided by Caitlin Trasande.

THE RETINA RECORDS THE LIGHT ARRIVING AT THE EYE

The neural retina, a thin, layered structure at the back of the eye (Fig. 16-5C), transforms incident light into neural activity that eventually results in perception of visual images. Here we focus on just three topics concerning retinal function:

- Photoreceptor types and function
- Ganglion cell types and function
- Regional distribution of photoreceptors and ganglion cells

The photoreceptors are sensory receptor cells—they transduce light. We focus on photoreceptors because these cells are at the center of a number of clinical issues, several of them common. Photoreceptors pass information onto bipolar cells, which in turn synapse onto retinal ganglion cells. We focus on ganglion cells because specializations seen in ganglion cells presage the division of labor observed in downstream visual pathways. Finally, regional variations in retinal structure and function underlie our variable sensitivity to images across the visual field. Unfortunately, even as we gain depth by restricting our discussion to photoreceptors and ganglion cells, we leave out a great deal of fascinating biology.

PHOTORECEPTORS SIT AT THE END OF THE LIGHT PATH IN ORDER TO INTERACT DIRECTLY WITH THE PIGMENT EPITHELIUM

Box 16-10

THE SCLERA FORMS THE WHITE OF THE EYE IN FRONT AND IS CONTINUOUS WITH THE DURA MATER IN THE BACK.

The sclera is a tough outer membrane and its outer layers are continuous with the dura mater that extends from the diencephalon to ensheath the optic nerve. The inner portion of the sclera joins with the choroid to form a vascularized region between the retina and the sclera/dura.

After passing through the length of the eye, light finally hits the retina (Fig. 16-5). Light then passes through most of the retina to reach the photoreceptors (Fig. 16-5C). Even upon reaching photoreceptors, light passes through the synaptic terminals and somata of the photoreceptors before arriving at the photoreceptors' outer segments, where light-sensitive molecules are densely packed (Fig. 16-11A). Although it may seem puzzling at first that the light-sensitive part of photoreceptors lies in the deepest part of the retina and farthest away from the light source, this arrangement is necessary because photoreceptors *require direct interactions with the pigment epithelium*, the non-neural outer layer of the retina (see Box 16-11), for continued function as detailed below. The neural retina and the eye in front of it are relatively transparent, allowing light to pass nearly unimpeded to the photoreceptor outer segments.

The pigment epithelium is a single layer of retinal cells containing pigments called **ocular melanins** (see Box 16-12). The choroid, a vascularized epithelial tissue deep to the pigment epithelium is also pigmented, appearing black or nearly so (Fig. 16-11A). The dark lining of the eye functions as does the darkened interior

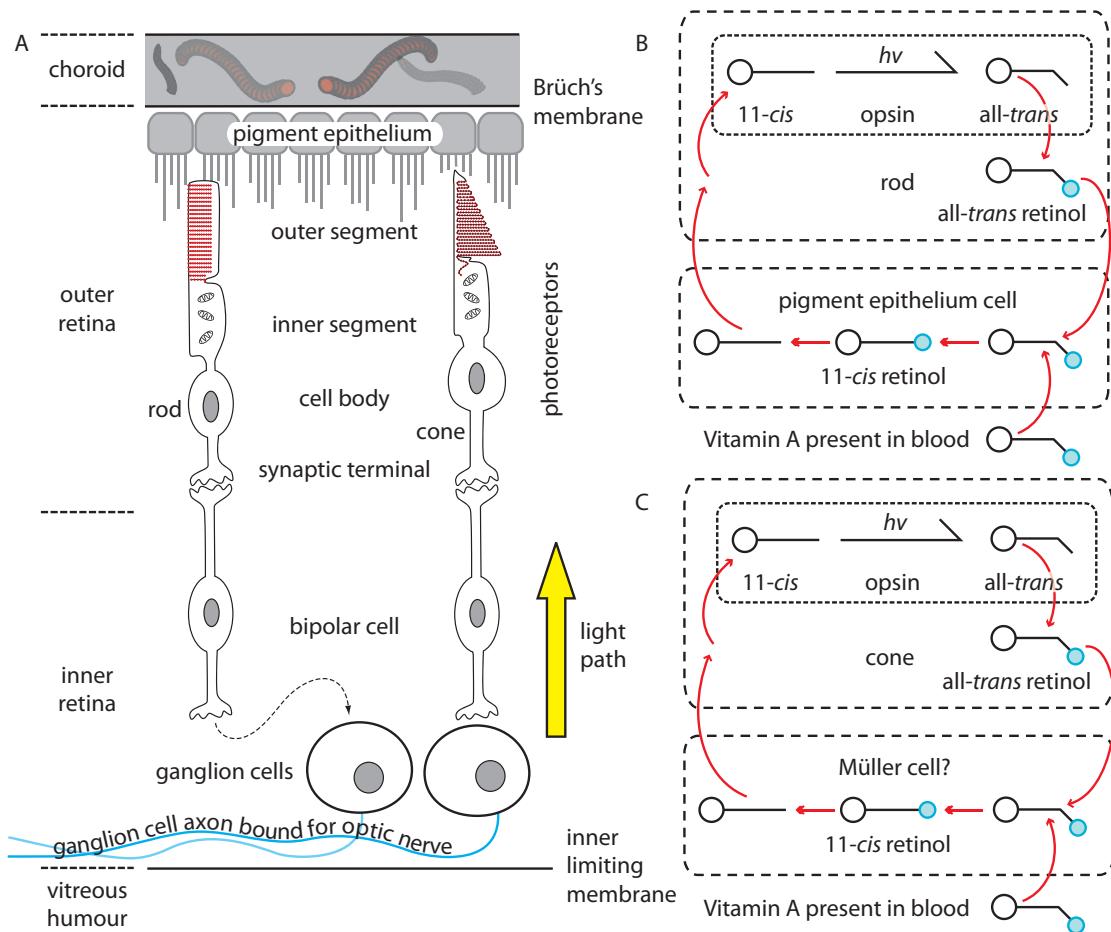


Figure 16-11. A: The retina is a layered half-globe structure at the back of the eye. The part of the retina closest to the back of the eye is the outer retina, and the layers closest to the inside of the globe, occupied by vitreous humor, comprise the inner retina. After light passes through the vitreous humor, it first passes through a layer of ganglion cell axons and cell bodies. The ganglion cells, which are the output of the retina, send an axon toward the optic disk. The unmyelinated ganglion cell axons collect at the optic disk and become myelinated as they form the optic nerve. As a result, myelin does not interfere with the path traversed by incoming light. After passing through layers of ganglion cells and bipolar cells, and through the cell bodies and inner segments of photoreceptors, light finally reaches the outer segments of the photoreceptors. Within the outer segments, stacks of membranous discs either continuous with the plasma membrane (cones) or located completely intracellularly (rods) house an enormous number of rhodopsin molecules (red dots), each ready to catch a photon. Photoreceptor outer segments are embedded in the microvilli, thin processes, of retinal pigment epithelial cells. Pigment epithelial cells contain melanin pigments that absorb light, minimizing the number of photons that can reflect off the back of the eye and stimulate photoreceptors on the rebound, thereby diffusing the image. Deep to the pigment epithelium is the choroid. The inner layer of the choroid is **Brück's membrane**. The choroid is heavily pigmented and therefore can absorb the small amount of light that makes it through the sclera, vitreous humor and retina. With age, **Drusen**, hard accumulations of extracellular material, accumulate between Brück's membrane and the pigment epithelium. Too much Drusen interferes with nutrient and waste exchange between the choroid and the retina and is a major contributor to age-related **macular degeneration** (see Box 16-17). B: When a molecule of rod rhodopsin catches a photon ($h\nu$), 11-cis retinal is converted into all-trans retinal and the rhodopsin molecule is activated. **Rhodopsin kinase** is an enzyme that inactivates rhodopsin containing all-trans retinal. All-trans retinal is then transported out of the opsin and converted into **all-trans retinol** by **retinal dehydrogenase**. Note that all-trans retinol is synonymous with vitamin A and is available both from the photoreceptor and from blood. All-trans retinol is transported out of the rod and into the pigment epithelium. Within the pigment epithelium, all-trans retinol is isomerized into 11-cis retinol and then into 11-cis retinal. It is 11-cis retinal that is then transported out of the pigment epithelium and back into the rod, where it is inserted into an opsin and available for photoisomerization. C: The cycle of renewal for retinal in cones is similar to that in rods except that glial cells called **Müller cells** rather than pigment epithelial cells appear to do the re-isomerization.

Box 16-11

BOTH THE NEURAL AND NON-NEURAL PARTS OF THE RETINA DEVELOP FROM A DIENCEPHALIC OUTPOUCHING.

The eye develops from a diencephalic outpouching termed the optic vesicle (see Fig. 3-2). Interactions between the optic vesicle and overlying ectoderm induce the lens placode. The optic vesicle grows to form a pocket, the **optic cup**, within which the lens and vitreous humor will eventually sit. The optic cup becomes the retina, sandwiched between the vitreous humor and the choroid epithelium. The back leaflet of the optic cup becomes the retinal pigment epithelium, and the front leaflet becomes the neural retina. Since pigment epithelial cells derive from neuroectoderm and are not neuronal, one can view them as a type of glial cell, in this case specialized to support photoreceptor cells.

of a camera: light is absorbed and therefore does not bounce around. The darkened choroid and pigment epithelium prevent light from reflecting off the back of the eye and returning to “hit” the photoreceptors for a second time, creating blur and ghost images.

Beyond the optical advantages that they confer, *pigments at the back of the eye absorb a great deal of energy by absorbing light* (see Box 16-13). This prevents the cellular damage that would otherwise be caused by the dangerous combination of light and oxidation. The most damaging light in this regard is higher-frequency or shorter-wavelength lights, mostly blue, violet, and ultraviolet light. The lens filters out most of the ultraviolet light. The pigment epithelium, like the macula lutea, contains lipofuscin, which acts like biological sunglasses to absorb damaging short wavelength light.

PHOTORECEPTORS COME IN TWO VARIETIES

Photoreceptors come in two varieties: rods and cones. There are three types of cones specialized to respond to light of different wavelengths, as described in detail below. Both rods and cones have an outer segment, the segment closest to the pigment epithelium at the back of the eye, where phototransduction occurs, an inner segment where energetic housekeeping occurs, a cell body containing the nucleus, and a synaptic terminal (Fig. 16-11A). The outer segment of both cell types contains rows and rows of **discs**, membranes that house the visual pigments responsible for phototransduction.

Principal among the important differences between rods and cones is the far greater sensitivity of rods than cones to light. As a result, only rods mediate vision under the dimmest light conditions, such as those on a cloudy night in the country, termed **scotopic** conditions. In light bright enough to see vibrant colors, rod responses are saturated and cannot signal any further differences in luminance. Therefore, during bright, colorful conditions, termed **photopic** conditions,

Box 16-12

ALBINOS LACK OCULAR PIGMENT, RESULTING IN VISION OF POOR ACUITY.

Albinism is an inherited condition characterized by the inability to synthesize pigment. Albinos lack pigment in all eye tissues. Although we may not think of our sclera as pigmented, it does in fact contain pigment that is opaque and white in color. Albinos lack sclera pigment and therefore light penetrates through their sclera and hits the retina without being focused by the cornea and lens. As a consequence,

light hitting an albino’s retina is diffuse and unfocused. The inherently diffuse light projecting onto the retina greatly impairs the vision of albinos. In addition, since albinos grow up seeing unfocused images, they have greatly reduced visual acuity and abnormal eye movements even as adults (see Box 16-32 for a discussion of the development of vision).

RETINAL DETACHMENT IRREVERSIBLY DAMAGES VISION.

The retinal pigment epithelium is critical to photoreceptor function in part because it absorbs potentially damaging light energy. The pigment epithelium is also critical as it ferries nutrition and waste between the choroidal blood vessels and the neural retina. Due to the critical interactions between the pigment epithelium and the neural retina (more such interactions are described in the text), any separation between the two, a condition termed **retinal detachment**, has dire consequences. Retinal detach-

ment often results from a physical trauma such as a blow to the head or eye surgery. It can also occur as a complication of *diabetes mellitus*. Once started, detachments have the tendency to spread, with the retina peeling off like paint from a wall. Since we currently know of no way to reattach the retina to the pigment epithelium, current treatment strategies are aimed at preventing additional regions of separation and therefore further visual impairment.

vision depends exclusively on cones. During intermediate light or **mesopic** conditions, present in a dimly lit restaurant, at dawn or twilight, when colors are visible but appear muted, both rods and cones respond to light and contribute to vision.

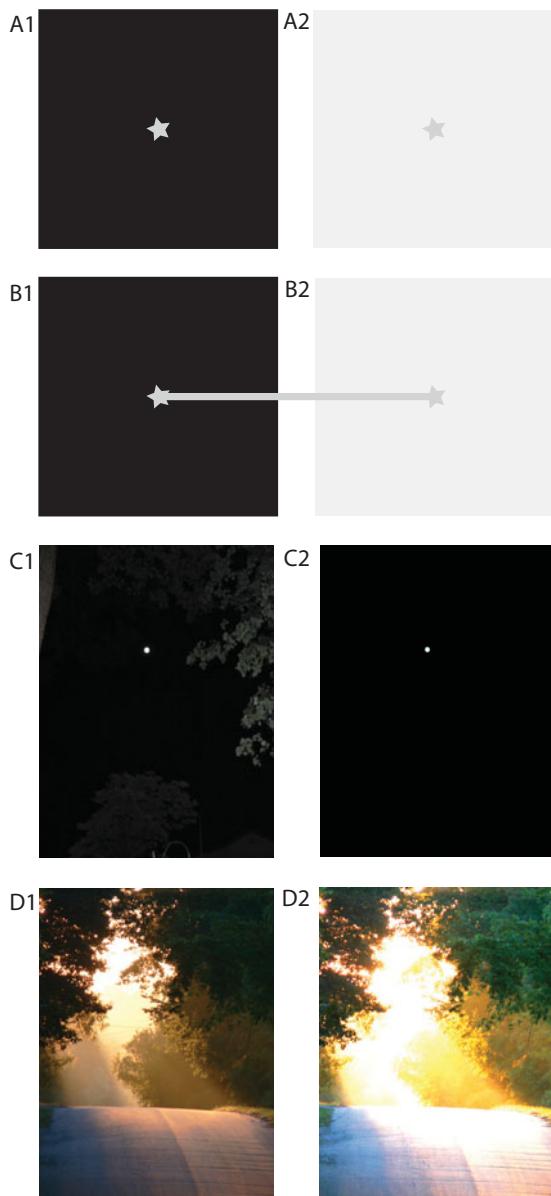
MODULATORY MECHANISMS ALLOW US TO SEE IN CONDITIONS THAT RANGE FROM NEARLY COMPLETE DARKNESS TO A BRIGHT SUNNY DAY

One of the most remarkable features of vertebrate vision is the wide range, *more than ten log units*, of intensities over which it operates. Think of the difference between navigating among the furniture in a dark room and reading outside on a bright summer day. As predicted by Weber's law (see Chapter 15), we are sensitive to small changes in dim light while being insensitive to those same small changes in bright light. In bright light, we react to much brighter lights just as we do to dim lights in the dark. In essence, rather than responding to light at some absolute level of intensity or even to a change in light intensity of a set magnitude, *the visual system reacts to stimuli that are different enough from the background to stand out* (Fig. 16-12). Put in other words, the visual system supports responses to any stimulus with a sufficient stimulus-to-background intensity ratio.

Part of the flexibility in reacting to light intensity over such a large range derives from having two different systems: one based on rods, which operate alone during scotopic conditions, and one based on cones, which operate during photopic conditions. Even so, rods and cones each operate over more than 5 log units of light intensity. This is paradoxical, as individual rods and cones can only code for, or have a meaningfully different response to, no more than 2 log units of light intensity at any one moment. So, if the photoreceptor response saturates after a 50–100 times increase

Figure 16-12. Adaptation serves to maximize sensitivity in dim light conditions while also maintaining sensitivity to nonsaturating levels in bright light conditions. The light star in the center of the black square (A1) stands out far more than the one in the middle of the white square (A2). Yet, both stars have the same luminance, a fact that is easily visualized when a line of equiluminance joins the stars (B1–2). The perceived brightness of the light star is far greater when placed within the dark square than within the white square because of Weber's law (see Chapter 15); the ratio of the star's luminance to the background luminance is far greater in the case of the black square than in the case of the white square. Because of adaptation, we see objects with a sufficient signal-to-background ratio rather than objects with any particular luminance threshold. In the moonlit picture (C1), we see the outline of a tree in the upper left and leaves on the right and at the bottom, as well as a bright moon. However, in the absence of adaptation (C2), we would only see the moon. In the sunlit picture (D1), we see detail and graded brightness in both the dark and light portions of the scene. On the other hand, without adaptation (D2), the brightly lit middle portion of the scene would saturate, greatly decreasing the perceived visual texture and detail of the scene.

Photographs in C–D kindly provided by Gisèle Perreault.



in light intensity, how do we view objects that range over more than 10 log units of light intensity? The answer is adaptation, a general feature of all sensory systems, which enables high sensitivity at low-stimulus intensities and a far lower, nonsaturating sensitivity at high-stimulus intensities. For vision, adaptation means that in the dark, sensitivity is increased and in the light, sensitivity is diminished. Visual adaptation is accomplished in the retina by two primary mechanisms:

- Postreceptor adaptation
- Receptor adaptation

Postreceptor adaptation involves circuits in the inner retina, the retinal layers deep to the photoreceptors (closer to the vitreous humor). Postreceptor adaptation can occur quickly and is the dominant mode of adaptation at the low end of both rod and

Box 16-14

VITAMIN A DEFICIENCY IS A MAJOR CAUSE OF BLINDNESS IN DEVELOPING COUNTRIES.

Vitamin A, the substrate for retinal synthesis, is an absolute requirement for normal vision. Individuals deficient in vitamin A develop a number of eye and skin problems. Often, the earliest symptom associated with vitamin A deficiency is **night blindness**, an impairment of vision in scotopic conditions, due to a lack of retinal in rods. Persistent vitamin A deficiency will eventually cause total blindness when cones stop functioning due to the lack of available retinal. Persistent vitamin A deficiency also impairs tear production, resulting in severe **xerophthalmia** or dry eyes, and causes a number of changes in the cornea that eventually lead to the irreversible destruction of the cornea. Vitamin A deficiency is a major problem and cause of blindness in poorer nations. Moreover, although not an issue among the well-nourished, vitamin A deficiency is on the rise within the United States, particularly among populations whose nutritional intake does not regularly include fresh vegetables and fruits.

Box 16-15

RHODOPSIN IS A RETINAL-CONTAINING OPSIN.

Rhodopsin is the only term for the specific photopigment contained in rods. Rhodopsin is also a generic term for any retinal-containing opsin, including that in cones.

cone intensity ranges. As light intensity increases, both rods and cones engage mechanisms of receptor adaptation, which involve modifying the sensitivity of molecules involved in phototransduction. Targets of receptor adaptation include photopigment, molecules involved in the outer segment's signaling cascade, and ion channels. As a result of adaptation, a **dark-adapted retina**, one that has been in total darkness for a while, is *exquisitely* sensitive to light. In fact, Jeremy Nathans calculated that a person adapted to the dark can detect a flash of light containing “the potential energy [equivalent to that] lost by dropping a single *Escherichia coli* [bacterium] 2 mm,” a sensitivity entirely attributable to rod function (Nathans 1994).

A minor contribution to maintaining sensitivity in scotopic conditions, while preventing saturation at photopic conditions, is pupillary size. The pupil is largest in the dimmest light and smallest in the brightest conditions. Reducing pupillary size decreases the light falling on the retina relative to the light incident on the cornea, but only modestly.

BOTH RODS AND CONES USE A VITAMIN A DERIVATIVE TO TRANSDUCE LIGHT ENERGY INTO ELECTRICAL ENERGY

All of our photoreceptors contain the same light-absorbing molecule or **chromophore**: retinal. Retinal is derived from the alcohol **retinol** or **vitamin A**, which must be ingested through the diet (see Box 16-14). Retinal fits within a protein called an **opsin** and the retinal-containing opsin forms a metabotropic receptor (see Chapter 8) called **rhodopsin** (see Box 16-15). The particular opsin in each rhodopsin determines the optimal wavelength of light that the rhodopsin absorbs (Fig. 16-13). One opsin is contained in the single type of rods, whereas three different **iodopsins** are contained in each of three different types of cones:

- Rod opsin or rhodopsin (peak absorption of light with wavelength of ~496 nm)
- Iodopsin in L (for long wavelength) cones (~560 nm)
- Iodopsin in M (medium wavelength) cones (~530 nm)
- Iodopsin in S (short wavelength) cones (~420 nm)

For all rhodopsins, the ligand is not a neurotransmitter but rather light.

Retinal exists in two conformations: 11-cis and all-trans. In the dark, retinal is in the 11-cis conformation (Fig. 16-11B-C). When rhodopsin *catches* or absorbs a photon, retinal changes its conformation to all-trans and rhodopsin becomes activated. This change in conformation triggered by light is termed **photoisomerization**. Activated rhodopsin, like other activated metabotropic receptors, activates a G protein, which in this case is called **transducin** (see Fig. 8-6). In fact, each

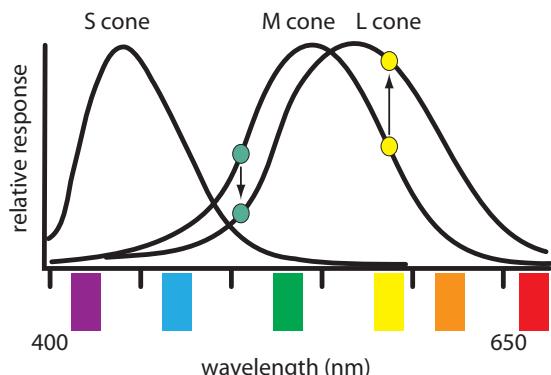


Figure 16-13. Humans have three different cones that respond optimally to different wavelengths of light. Although the three cones respond best to different peak wavelengths, their tuning curves are broad and so they respond, with higher or lower probability, to a range of wavelengths. Thus, the response of any one cone type does not unambiguously signal wavelength. For example the M cone's responses to wavelengths typically perceived as turquoise and yellow are about the same. Yet, we easily tell turquoise from yellow, in part because the L cone responds far better to long wavelength light (usually seen as yellow) than to medium wavelength light (usually seen as turquoise), and in part because the S cone responds only to medium wavelength and not to long wavelength light. Using the responses of the three different cones, colors across the visible spectrum can be distinguished as unique combinations of the three cone responses.

activated rhodopsin activates hundreds of transducin molecules. The activated α subunit of transducin then activates phosphodiesterase E, which hydrolyzes cyclic guanosine monophosphate (cGMP), leading to a decrease in the cytoplasmic concentration of cGMP. As long as phosphodiesterase E is bound to the activated α subunit of transducin, it continues to hydrolyze cGMP into GMP. Recall that photoreceptors have a resting, *in the dark*, inward current that uses a nucleotide-gated ion channel, the cGMP-gated ion channel (see Chapter 8). By decreasing the concentration of cGMP, light decreases the number of open cGMP-gated ion channels. Since cGMP-gated ion channels carry inward current, closing them leads to a *hyperpolarization*. Mutations in the genes for proteins involved in phototransduction are among a large heterogeneous group of genetic causes of *retinitis pigmentosa* (see Box 16-16).

There is a remarkably large response to just one photon. This results from two steps of amplification in the light-evoked signaling cascade:

1. Activation of transducin
2. Conversion of cGMP to GMP

Thus, *one* photon that activates *one* rhodopsin molecule leads to the activation of *hundreds* of G proteins (transducin molecules), a measurable reduction in the local concentration of cGMP, and ultimately the closure of *hundreds* of cGMP-gated cation channels.

RETINAL MUST BE RECYCLED IN ORDER THAT RHODOPSIN CONTINUES TO BE SENSITIVE TO LIGHT

For rhodopsin to respond to light, retinal must be in the 11-cis form. Therefore, after photoisomerization, a mechanism to switch retinal from all-trans back to 11-cis is needed (Fig. 16-11B-C). This means separating the retinal from the opsin, isomerizing the retinal to 11-cis, and returning it to an opsin, all of which takes energy. In fact, not only the energy necessary for isomerization but also energy for transport is required because photoreceptors cannot isomerize all-trans retinal into the 11-cis form.

In the case of rods, the pigment epithelium performs the crucial isomerization (Fig. 16-11B). Retinal from rod rhodopsin is converted into all-trans retinol, or vitamin A, which is transported out of the photoreceptor and into the pigment epithelium. The pigment epithelium converts all-trans retinol into 11-cis retinal, which it ships back to the rod outer segments. This cycle requires contributions from several enzymes and

RETINITIS PIGMENTOSA IS A DEGENERATIVE DISEASE OF PHOTORECEPTORS.

Retinitis pigmentosa is a diverse family of genetic diseases that cause a progressive loss of photoreceptor function, resulting ultimately in the death of photoreceptors and blindness. The disease is named for the pathological appearance of pigmented blotches in the retina. The majority of retinitis pigmentosa disease initially impacts rod vision, with night blindness and loss of peripheral sight comprising typical early symptoms. Eventually, sometimes at a much later time point, cones die and central high-acuity vision is lost.

A large number of varied mutations are associated with retinitis pigmentosa, which is relatively common, affecting 1 in 4,000 people worldwide. Some of these mutations, for example those in the genes for rod opsin, rod cyclic guanosine monophosphate (cGMP)-phosphodiesterase subunits, proteins involved in retinal recycling, or proteins important in vitamin A metabolism make some sense in that they have functions critical to photoreceptor physiology. Consider a defect in the cGMP-phosphodiesterase. An inability to activate cGMP-phosphodiesterase would lead to persistently high levels of cGMP and in turn constitutively open cGMP-gated ion channels, which would in turn cause excessive cation influx. Cation influx, likely including influx of calcium ions, may injure and eventually kill rods. As another example, mutations in the rod opsin gene, accounting for 25% of retinitis pigmentosa cases, appear to interfere with metabolism or the structure of the outer segments or may

cause harmful intracellular protein aggregates. Interestingly, just as high levels of intracellular calcium ions can kill photoreceptors, it appears that excessively low levels of calcium ions can also kill photoreceptors. This susceptibility may explain why continuous light exposure causes blindness in animals. Recall that light reduces the influx of cations, including calcium ions, into photoreceptors so that continuous light would be expected to be accompanied by a very low concentration of resting calcium ions.

In contrast to the “sensible”—or within the realm of sensible—mutations mentioned above, some mutations associated with retinitis pigmentosa affect universal processes with no particular or exclusive connection to photoreceptor function. For example, mutations in genes that code for enzymes that splice out introns or for a particular pH-regulating enzyme, carbonic anhydrase IV, are associated with retinitis pigmentosa. Understanding how such mutations specifically affect photoreceptors is an exciting challenge for future investigators.

Patients with retinitis pigmentosa benefit from aggressive treatments to optimize vision—visual aid devices, cataract removal, and so on. Although no well-established and effective treatment exists for all or even a large proportion of patients, a number of genetic therapies aimed at restoring absent proteins coded for by genes with recessive mutations or at inactivating defective proteins coded for by genes with dominant mutations have been tried with some success.

binding proteins and takes minutes to accomplish. Furthermore, it renders the rods completely dependent, on a short time scale, on the pigment epithelium. Without the pigment epithelium, rods would stop operating in short order.

The process by which retinol from cone rhodopsins is recycled is not as well understood as the process for recycling retinol from rods. Yet, we know that recycling cone retinol occurs largely independently of the pigment epithelium. Instead, cells in the neural retina, perhaps retinal glia called **Müller cells**, appear to convert all-trans retinol into 11-cis retinal (Fig. 16-11C). Therefore, cone function is less immediately dependent on pigment epithelium than is rod function.

DISCS LAST ABOUT TEN DAYS BEFORE BEING PHAGOCYTOSED BY THE PIGMENT EPITHELIUM

The retina is particularly oxygen-rich as it extracts about half of the oxygen arriving in the choroidal arteries. Coupled with the high concentration of oxygen, photon bombardment renders the retina highly susceptible to oxidative damage. To minimize oxidative damage of photoreceptors, discs and their component molecules are renewed every ten days. This renewal ensures against molecules “going bad” and errantly failing to function or functioning inappropriately in the absence of light. The disc renewal cycle operates on discs of both rod and cone outer segments.

The opsins contained in photoreceptor discs are synthesized in the inner segment and then incorporated into the plasma membrane at the base of the outer segment. Discs form from this plasma membrane, either budding off in the case of rods or simply forming repeated invaginations in the case of cones (Fig. 16-11A). As newer discs form, the older ones move outward toward the tip of the outer segment. The oldest discs contain the highest concentration of free radicals and proteins damaged by light and oxygen. Each day, the pigment epithelium phagocytoses the tips of the outer segments, containing the last several rows of discs. The pigment epithelium’s central role in the disc renewal cycle is another reason why retinal function is completely dependent on being in contact with a healthy pigment epithelium (see Box 16-17).

THE PRESENCE OF MULTIPLE CONE TYPES ALLOWS FOR COLOR VISION

Color vision depends on the presence of at least two different photoreceptor types that respond maximally to light of different wavelengths (see Box 16-18). Humans with normal color vision have in fact *three* different cone types containing *three* different photopigments. Human cones maximally absorb wavelengths in different ranges:

- Long-wavelength or L cones (~560 nm)
- Medium-wavelength or M cones (~530 nm)
- Short-wavelength or S cones (~420 nm)

The absorption spectra of L and M cones are very similar (Fig. 16-13) because the protein sequences of the two iodopsins are very similar. The genes for these similar iodopsins sit next to each other on the X chromosome, and one probably arose from the other through gene duplication in an early primate. Having two cones with similar but distinct absorption spectra in the medium- to long-wavelength range may have facilitated picking out ripe yellow and red fruit from the surrounding green vegetation.

AGE-RELATED MACULAR DEGENERATION RESULTS IN A SEVERE DEGRADATION OF CENTRAL VISION.

Age-related macular degeneration is a heterogeneous disease that results in the deterioration of the central portion of the retina, the **macula**, and consequently a loss of central vision (see text for more on the macula). In some individuals, macular degeneration results from inflammation and in others from an excess of **angiogenesis**, or blood vessel formation, in the choroid. Yet, in most cases, the culprit is a disruption of the delicate but required partnership between the pigment epithelium and photoreceptor outer segments. Discs within the photoreceptor outer segments are vulnerable to damage from both free radicals and from light. The pigment epithelium defends against these vulnerabilities by phagocytosing the oldest discs on a daily basis, absorbing damaging blue light, and neutralizing oxidative

damage through the production of antioxidants. Unfortunately, with age, lipofuscin appears to accumulate to toxic levels in the pigment epithelium. The resultant culling of pigment epithelial cells means that each remaining pigment epithelial cell now needs to phagocytose more outer segments, clear more damaged proteins, and neutralize more free radicals. Pigment epithelial cells die from this cellular stress, leaving behind yellow deposits called **Drusen** that are pathognomonic for macular degeneration. The macula is most severely affected, perhaps because it is lipofuscin-rich and more energetically active than the peripheral retina. Age-related macular degeneration is the most common cause of blindness in industrialized countries, and most existing therapies are aimed simply at preventing progression.

The absorption peaks for cone iodopsins do not represent the *response profiles* of cones to different wavelength light. The absorption spectra are broad, meaning that wavelengths far from the peak still elicit a response (Fig. 16-13). For example, an S cone with an absorption peak of about 420 nm may respond to wavelengths as long as 540–550 nm. Furthermore, a cone's response bears no information about the wavelength of the captured light. Consequently, regardless of the incident wavelength that excites a cone, the cone's response is the same. Thus, a cone response is a cone response and contains *no information about wavelength*.

Since the responses of any one cone do not carry information about wavelength, the responses of one cone class cannot support color vision. To understand why multiple cones are needed to discriminate between different colors, consider M cones, which absorb and respond maximally to light with a wavelength of about 530 nm. As the response of photoreceptors is *probabilistic* (see Chapter 15), M cones respond to light with wavelengths greater than or less than 530 nm, only with a lower likelihood than they do to light of the optimal wavelength. Thus, light with a wavelength of about 510 nm, typically perceived as aqua, and light with a wavelength of about 590 nm, typically perceived as yellow, excite M cones to roughly the same degree (Fig. 16-13). This means that if we only had information from M cone responses, a banana would be perceived as the same color as a piece of turquoise. Yet, we easily tell the difference between yellow and turquoise. In part this is because light with a wavelength of 590 nm, perceived as yellow, stimulates L cones near maximally whereas light with a wavelength of 510 nm, perceived as aqua, stimulates L cones poorly. Thus, the ratio of L cone to M cone responses, abbreviated as the **L/M ratio**, is greater than 1 in the case of the 590 nm light and less than 1 in the case of the 510 nm wavelength.

COLOR PERCEPTION IS TRULY AN INDIVIDUAL EXPERIENCE.

Color blindness refers to a group of disorders in which one or more of the cone pigments are defective. To understand these disorders, recall that the genes for medium- and long-wavelength iodopsins are arranged in tandem on the X chromosome. Since males have only one X chromosome and females two, far more males—about 2% of the Caucasian population—than females lack either medium- or long-wavelength iodopsin. Those without a medium- or long-wavelength iodopsin, affected individuals cannot distinguish between different wavelengths over about 550 nm. Such **dichromatic** individuals can discriminate short-wavelength light from light of longer wavelengths but cannot distinguish between what the rest of us perceive as red, orange, yellow, and green.

The M and L iodopsin genes are 98% identical at the nucleotide level. Therefore, homologous recombination often occurs between them. As a consequence, many individuals make a hybrid M-L iodopsin that moves the peak absorbance of either opsin toward that of the other. In these individuals, the L-M channel has a narrower range and as a result, long-wavelength lights are poorly distinguished.

The most common types of color blindness are:

- **Deutanopia** refers to a loss of M cone function. Deutanopes can distinguish short-wavelength light from longer-wavelength light, which activates the intact L cones, but wavelengths above 550 nm all activate the same L cone population, and thus are perceived as one color.
- Individuals with **protanopia** have no L cone function. Like deutanopes, protanopes can distinguish short-wavelength light from longer-wavelength light. However wavelengths greater than 550 nm only activate M cones and therefore are indistinguishable.
- **Deuteranomaly** is the most common type of color blindness, affecting about 5% of males. In affected individuals, L cone function is normal whereas M cones contain a hybrid opsin with its peak absorption shifted toward longer

wavelengths. Therefore, deuteranomaly results in **anomalous trichromacy**, with the distinction between wavelengths over 550 nm often, but not always, compromised.

- **Protanomaly** involves a hybrid L iodopsin with an absorption shifted toward shorter wavelengths and normal M cone function. Affected individuals, like those with deuteranomaly, are trichromats who often have a compromised ability to distinguish between wavelengths over 550 nm.

Additional variations in color vision exist but are far rarer than those listed above. For example, some individuals lack both M and L cone function and are consequently monochromats, dependent solely on S cone function for photopic vision. Another rare variation is the loss of S cone function, termed **tritanopia**. Since the short-wavelength iodopsin is coded by a gene on an autosomal chromosome, men and women are equally unlikely to suffer from tritanopia.

An inability to distinguish between long wavelengths puts a person at risk for mistaking a red traffic light for a green one. Such a potentially lethal error is a particular concern at night, when there is no surrounding context to differentiate red from green light. Additionally, different colors may appear to go together well only in the eyes of individuals with different iodopsin complements. Therefore, the next time you are tempted to “correct” a boy’s drawing of red grass or a man’s garish (to you) outfit, remember that you and he may be living in differently colored worlds. Finally, deficits in color vision diminish the vibrancy and excitement of certain scenes, such as the turning of the leaves in autumn.

Even beyond actual deficits in color vision, the large number of M and L iodopsin variations means that few of us share precisely the same perception of color. Indeed, the philosophical take-home message is that, as we all search for proverbial greener grass, we may not find it at the same wavelength.

In essence, by signaling whether a wavelength is closer to the absorption peaks of M or L cones, the L/M ratio is critical to distinguishing between different wavelengths longer than 550 nm, about the longest wavelength light to which S cones respond appreciably.

Two other bits of information in addition to the L/M ratio are used by the brain to estimate the wavelength of incident light. First, the combined responses of L and M cones, abbreviated as **L+M**, provide an estimate of overall luminance. Second, retinal circuitry calculates the difference between the response of S cones and the overall luminance, abbreviated as **S-(L+M)**. Short-wavelength light, commonly perceived as blue, will result in a positive value of $S-(L+M)$, whereas light with a wavelength greater than about 500 nm will result in a negative value of $S-(L+M)$. Thus, the value of $S-(L+M)$ is an indication of how close a wavelength is to the peak wavelength of either the S cone or the L and M cones.

In sum, retinal circuitry transforms information from the three types of cones into three channels of information that the brain then uses to assign the percept of color to different wavelengths in the visual scene (Fig. 16-14):

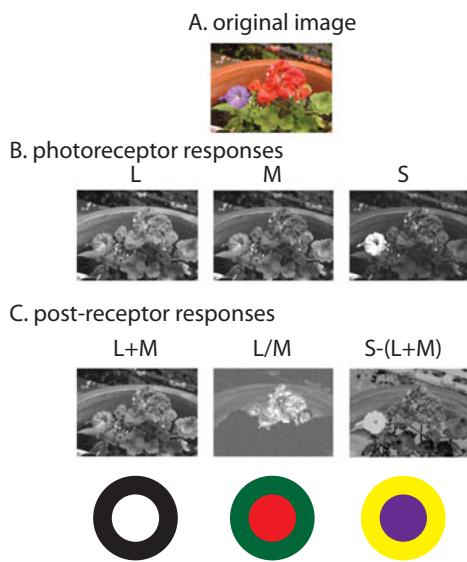


Figure 16-14. An analysis of how photoreceptors and ganglion cells of the three color channels would respond to an image of violet and red flowers with green foliage (A) is shown. B: The maximal responses of the three cone types are in white. S cones respond almost exclusively to the violet bloom. L and M cones respond similarly to both the green foliage and the red flowers. C: Information from the three cones is fed into three channels of color information. The L+M channel carries luminance information gained from the sum of L and M cone inputs. The L/M channel carries the ratio of L to M responses. This channel, unlike the responses of either L or M cones, clearly highlights the areas perceived as red over those that we perceive as green. The final channel, S-(L+M), carries the blue/violet signal. In the bottom row, the center-surround receptive field organization of retinal ganglion cells is shown. M ganglion cells have opposing responses to light and dark and carry the luminance (L+M) channel. P ganglion cells have opposing responses to medium- and long-wavelength light (L/M channel). K ganglion cells carry the S-(L+M) channel with opposing responses to yellow and violet/blue.

This figure is modified from Shevell, S.K., and Kingdom, F. Color in complex scenes. *Ann Rev Psychol* 59:143–66, 2008, with permission of the publisher, Annual Reviews.

- L/M ratio or L-M
- L+M or luminance channel
- S-(L+M) cone channel

Any wavelength that falls on the retina produces a unique combinatorial signature in the three channels. Light of different wavelengths produces different combinations of activity in the three color channels. The brain then uses a combinatorial code to estimate the wavelengths of incoming light. Table 16-1 shows how activity in the three channels compares for six wavelengths across the visible spectrum. In sum, *light of any wavelength produces a unique combinatorial signature in the three channels*.

Thalamic and ultimately cortical circuits build upon the same three channels of color information initially set up by retinal circuitry in order to decipher color information from the visual world. Single retinal neurons embody the channels described above by showing excitatory responses to light with certain characteristics in a central region and inhibitory responses to light with opposing characteristics in the surround region. For example, some cells of the luminance channel (L+M) are excited by broad-spectrum light, “white” light, in the center and inhibited by a lack of luminance, black, in the surround region of the receptive field (Fig. 16-14). Other cells in the luminance channel are excited by a lack of luminance in the center and inhibited by light in the surround. Additional modulatory information, about form, motion, expectation, and a myriad of other factors can alter the color perceived even when the wavelength of the object remains steady (see Box 16-19). Color perception’s dependence on local comparisons is likely coded for by thalamocortical circuits that use

TABLE 16-1. LIGHT OF WAVELENGTHS ACROSS THE VISIBLE SPECTRUM ARE PERCEIVED AS DIFFERENT COLORS

WAVELENGTH (NM)	PERCEIVED COLOR	L/M RATIO	L+M	S-(L+M)
420	Violet	0	0	>>0
470	Blue	<<1	very low	>0
530	Green	~1	high	<0
580	Yellow	>1	high	<<0
620	Orange	>>1	moderate	<<0
700	Red	>>1	low	<<0

The brain distinguishes different wavelength lights by comparing the activation produced in three “color” channels. Each wavelength produces a unique combination of activity in the three channels

the three color channels emanating from the retina along with additional modulatory input.

ROD-DEPENDENT VISION DIFFERS MARKEDLY FROM CONE-DEPENDENT VISION

Key differences between rods and cones drive profound differences between the types of vision supported by the two types of photoreceptors. The key differences between rods and cones and between rod- and cone-supported vision include:

- Due to a higher number of photopigment molecules and to greater signal amplification, *rods are more sensitive to light than are cones*. Thus, rods respond when a single photon hits one rhodopsin molecule whereas cones have a higher threshold.
- *Rods have slower responses to light than do cones*, making them poor at resolving temporal changes such as flicker. For instance rods can only detect flicker at 12 Hz or less, whereas cones detect flicker at rates up to about 55 Hz.
- *Rods do not support high-acuity vision* but are capable of making out rough shapes. We cannot read small type using our rods. In contrast, cones respond best to a point of light centered upon them. *Cone-mediated vision allows us to detect fine visual details but is poor at finding a dimly lit star in the sky*.
- Because there are three cone types, each containing a photopigment optimized to absorb light of a different wavelength, cones support color vision.

Box 16-19

COLOR PERCEPTION DEPENDS ON FACTORS BEYOND WAVELENGTH.

The wavelength of incident light influences but does not unalterably determine the perception that we call color. The color that we perceive depends in part on wavelength but also on the wavelengths emanating from surrounding objects, the overall luminance of the scene, and even expectation.

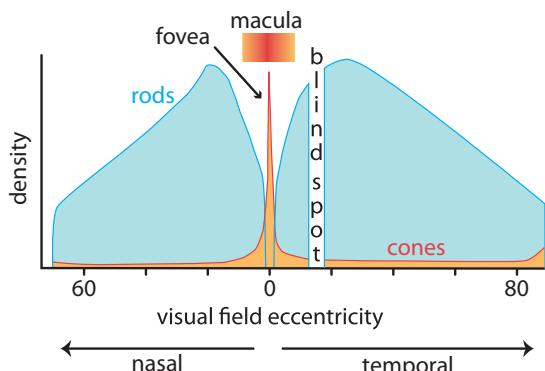


Figure 16-15. The spatial distribution of rods and cones across the retina is illustrated. The only region where cones outnumber rods is within the fovea, which is located at the sharp peak of cones. In fact, in the very center of the fovea, no rods are present, and cones reach their maximal density. The fovea forms the center of the macula. Outside of the fovea, even within the macula, rods outnumber cones. The optic disc, where retinal ganglion cell axons collect to exit through the optic nerve, is in the nasal part of the retina and receives light from the temporal visual field. The optic disc contains no photoreceptors at all, and thus no light is transduced in this area, termed the *blind spot*.

Rods, the only photoreceptor with high sensitivity to light, support **monochromatic** vision, meaning vision along a grayscale.

- Retinal circuits feed the responses of many rods onto a single ganglion cell, whereas input from very few cones, and in some cases a single cone, converges onto a single ganglion cell. This circuitry further exaggerates the high sensitivity and low resolution of rod vision and the high acuity of cone vision.
- Rods and cones are distributed differently throughout the retina, so that cones are concentrated in the center of the visual field and rods in the periphery (Fig. 16-15). This means that *our highest-acuity vision is at the point of fixation*. On the flip side, we can detect the dimmest lights only by looking slightly to the side and thereby aiming the dim light at the peripheral retina.

In sum, rod-supported vision is excellent for detecting low levels of light but not for tasks that require high acuity, such as reading. Cone-supported vision cannot operate in scotopic conditions but supports high-acuity vision as well as, of course, color vision (see Box 16-20).

THE CENTRAL AREA OF THE RETINA SUPPORTS HIGH-ACUITY VISION

Light from the very center of the visual field, the area of space that we “are looking at,” projects onto the **area centralis** or macula (see Box 16-1). At the center of the macula is the fovea, an indented region of the retina that contains

Box 16-20

INDIVIDUALS WITHOUT CONES SUFFER FAR MORE FROM A LACK OF HIGH ACUITY THAN FROM A LACK OF COLOR.

Congenital achromatopsia is a rare inherited disease in which cones do not respond to light. Mutations in genes for the cone cyclic guanosine monophosphate (cGMP)-gated cation channel and the cone isoform of transducin are two of several potential causes. Individuals with congenital achromatopsia view the world through rods alone. Consequently, these individuals have very poor visual discrimination in time—flicker—and space—form. As a consequence

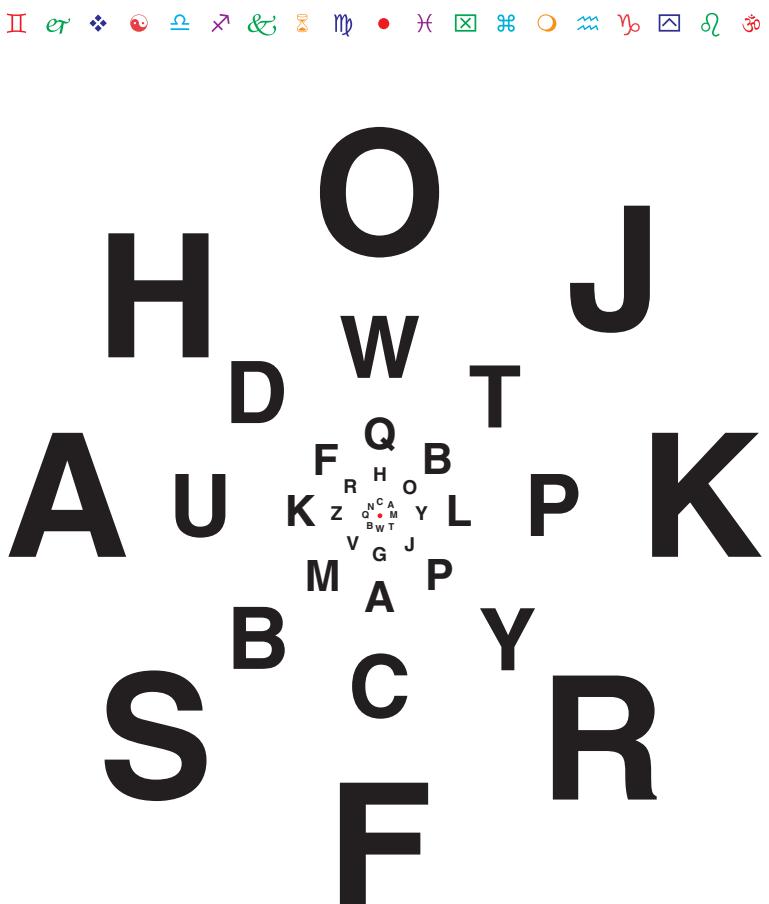
of vision’s dependence on normal development (see below) and the low-resolution information provided by a coneless retina, cortical circuits never mature normally. Therefore, individuals with congenital achromatopsia see the world in low resolution. Since the development of normal eye movements depends on focused images, people with congenital achromatopsia also have abnormal eye movements.

only cones. All retinal cell types except cones, including rods, bipolar cells, and ganglion cells, are displaced to the side. Because of the densely packed cones in the fovea, this central region of the retina supports the *very highest* acuity vision. Figure 16-16 contains two exercises designed to demonstrate how rapidly acuity falls off as the distance from the point of fixation increases. When you fixate on the red dot in the upper line of type, you are likely to be able to describe the shape and color of only one or two or maybe three symbols, to either side, of the fixation point. One of the most challenging parts of this task is to not cheat by shifting your gaze. Because of the rapid decline in acuity away from the retinal fovea, we have a dedicated system, the **oculomotor system**, to keep our fovea fixated on the part of the visual field of interest at any moment in time (see Box 16-21). Suppressing such eye movements, as in the exercise above, takes effort. Circuitry dedicated to keeping the fovea directed to points of interest will be discussed in Chapter 26 on gaze control.

Outside of the macula, our ability to make out visual detail is poor because there are relatively few cones (Fig. 16-15). Yet, rods are concentrated in the peripheral retina, the retina outside of the macula. In the retina as a whole, rods far outnumber cones by about 30 to 1. Excluded from the fovea, rods are densely packed into the peripheral retina, reaching their highest density at an **eccentricity** of about 15 degrees (see Box 16-22). Consequently, the best strategy to find a dim star on a dark night is to look about 15 degrees away from its expected location.

Figure 16-16. Visual acuity decreases dramatically in the peripheral visual field relative to the center of the visual field. Here, the polar skew in visual acuity is illustrated in two different ways. First, fix your gaze on the central red dot in the upper line of type. Now, try to describe the shape and color of the “wingdings” characters on either side. Second, fix your gaze on the central red dot in the chart below. How many letters can you read without shifting gaze? The size of the peripheral letters is related to the diminution in acuity at eccentric retinal positions.

Modified from Antis, S.M. A chart demonstrating variations in acuity with retinal position. *Vision Research* 14: 589-92, 1974, with permission of the publisher, Elsevier.



Box 16-21

THE TERM
OCULOMOTOR
SYSTEM REFERS TO
CIRCUITS INVOLVED
IN EXTRAOCULAR
MUSCLE CONTROL.

Up until this point, the term *oculomotor* has been used to refer to the nerve or nucleus of the third cranial nerve. The term oculomotor system, in contrast, refers to the circuits involved in controlling eye movements. One component of the oculomotor system is the oculomotor nerve and nucleus. Yet, the oculomotor system also includes the trochlear and abducens nerves and nuclei, the horizontal and vertical gaze centers, and additional regions such as the superior colliculus, frontal eye fields, and cerebellum. The oculomotor system is discussed in detail in Chapter 26 on gaze control.

Box 16-22

VISUAL ECCENTRICITY
REFERS TO THE
ANGULAR DISTANCE
OF A POINT FROM
THE VISUAL AXIS.

The visual axis is an axis that runs through the center of the pupil to the center of the retina, the fovea. Eccentricity refers to the polar distance from the fovea.

THE VISUAL FIELD ON ONE SIDE OF THE MIDLINE IS CARRIED TO THE CONTRALATERAL VISUAL CORTEX

Retinal ganglion cells send their axons out through the optic disc, located about 15 degrees medial to the fovea (see Box 16-23). Since there are no photoreceptors at the optic disc, this region is insensitive to light as evidenced by the *blind spot*. To find your right blind spot, close your left eye and fixate on the left-most symbol in Figure 16-16 (II) with your right eye. Then trace your finger or the point of a pencil slowly to the right. At some point, around the point of the \mathbb{X} or \textcircled{O} symbols, your finger will disappear. This marks your right eye's blind spot. You can reverse this process—close your right eye, fixate on the right-most symbol and trace your finger to the left to find your left blind spot. Tricks are needed to reveal the blind spot because normally we fill in any small hole in the visual field (see Box 16-24).

THE VISUAL WORLD IS BROKEN DOWN INTO CHANNELS CARRYING INFORMATION ABOUT DIFFERENT OPTICAL ATTRIBUTES

Although our perception of the visual world depends on the entirety of the visual images in front of us, *the brain breaks down the visual world before consolidating it back into a whole*. The retina does not fully process the visual scene but rather accomplishes some visual processing and transmits information to remote regions for further processing and ultimately image interpretation. Physically fitting retinal output within the small confines of the optic nerve further limits the amount of retinal processing of the visual signal. If the retina performed more processing and produced more output channels than it actually does, the optic nerve would need to be quite a bit larger than it is.

Retinal ganglion cells send information to the lateral geniculate nucleus, as well as to other areas involved in nonperceptual visual tasks as detailed below. In humans and other primates, there are close to two dozen output channels from the retina, each of which is carried by a distinct class of ganglion cells. Thus, the retina sends out many parallel channels of partially processed optical information. *Most of the channels carry information that is ultimately used for nonperceptual visual tasks.* Three primary channels, detailed below, are used by the thalamus and visual cortex to support perception. Thalamocortical circuits combine input detailing optical features to bring us a visual image. For example, primary visual cortex uses position and time information to detect edges. Additionally, information from both eyes converges for the first time on single cells in primary visual cortex, allowing for a calculation of object depth. In this way, each of the many ganglion cell classes carries a channel of information that codes for one or a few visual attributes.

Box 16-23

CHANGES IN THE APPEARANCE OF THE OPTIC DISC ACCOMPANY BRAIN SWELLING.

The optic disc caps the optic nerve, which emanates from the diencephalon (Chapter 3). As should be clear now, the retina is thus part of the central nervous system (CNS). And yet, the retina is accessible. The ocular window into the CNS is extremely valuable. The appearance of the retina is useful for diagnosing ophthalmologic diseases, such as macular degeneration, glaucoma, or optic neuritis. Further, the appearance of the optic disc in particular is a noninvasive tool used to check for an increase in intracranial pressure. The ability to check for brain swelling in this way is invaluable during an acute crisis when time is too short to allow for an imaging study.

There are four basic components, and numerous subcomponents, which comprise the neural representation of the visual image:

- Position and dimensions: where and how big
 - a. The location of an object in the flat visual field is described by its position, in polar coordinates, with respect to the center of the visual field at 0 degrees meridian and 0 degrees elevation.
 - b. The size of an object is typically thought of in terms of spatial frequency (see Chapter 15). Small detailed objects as well as sharp edges have a high spatial frequency, whereas large objects such as clouds have both low- and high-spatial-frequency components.
 - c. The distance from the viewer ranges from very close to optical infinity. Optical infinity refers to the distance, about 20–30 feet for humans, from which light travels in virtually parallel paths to reach the eyes (Fig. 16-7C).
- Form
 - a. Shape
 - b. Texture
- Color
- Motion
 - a. Direction
 - b. Velocity
- c. Temporal frequency refers to the changing appearance of an object across time. A steady light or an object that slowly moves has a low temporal frequency, whereas fireworks and lightning have a high temporal frequency.

Box 16-24

SCOTOMAS, OR HOLES IN THE VISUAL FIELD, ARE HARD TO DETECT WITH BOTH EYES OPEN.

Because most of the visual field strikes both eyes, a small hole in the visual field, termed a *scotoma*, will not be obvious as long as it is in the binocular part of the visual field and as long as both eyes are open. Even when viewing the world with only one eye, small scotomas often escape one's notice as the brain "fills in" the blank area. For this reason, computerized visual field testing, requiring the detection with one eye of points throughout the visual field, is typically necessary to uncover scotomas.

Most scotomas signal some pathology such as a stroke, a tumor, or the onset of a migraine; in the latter case the scotoma is transient.

All of us possess a scotoma at the point where the optic nerve exits the retina (see text). The fact that we are not aware of this physiological scotoma, the blind spot, demonstrates the brain's power to "guess" at what an image *should* look like and fill it in accordingly.

The nervous system processes the distinct channels in parallel. Cells in progressive positions along the visual pathways code for increasingly complex visual features. Retinal and lateral geniculate coding for spots of light yields coding for edges in the primary visual cortex. The coding of color also grows in complexity along the visual hierarchy as one moves beyond the primary visual cortex and into **extrastriate** cortex, visual cortical regions downstream from primary visual cortex. Information from separate channels combine to code for complex visual features. For instance, ovoid objects with some depth and certain embedded forms are recognized as human faces by neurons in inferotemporal cortex. For such recognition, the form channel may be most important but color, depth and indeed motion also contribute. In a similar fashion, cortex uses all visual cues, some more than others, to recognize the world and to move within it.

EVERY CHANNEL COLLECTS INPUT FROM ACROSS THE ENTIRE VISUAL FIELD

A ganglion cell *class* consists of ganglion cells with similar appearances, responses, and functions. The individual members of a ganglion cell class are distributed throughout the retina, so that they code for the same visual attribute or attributes from across the visual field. For example, the largest proportion of ganglion cells, about 70% of the ganglion cell population, are P ganglion cells (see Box 16-25). These cells have a small receptive field, meaning that they respond only to stimulation in only a small part of the visual field (see Box 16-26). In the fovea, the center of the receptive field of a P ganglion cell collects information from a single cone. P ganglion cells located more peripherally sum up the responses of several cones but still have a receptive field that is small, well under a degree of visual space. Because of their small receptive fields, many P ganglion cells are needed to cover the entire retina and thus the entire visual field. Therefore, P ganglion cells are located all over the retina, distributed like overlapping tiles. P ganglion cells also carry the L/M color channel. Due to their small receptive field, P ganglion cells are critical to form vision, for perceiving what objects are in view, and thus contribute heavily to the ventral visual stream.

Box 16-25

RETINAL M AND P GANGLION CELLS ARE NAMED FOR THEIR PROJECTION TARGETS.

Retinal **M** and **P** ganglion cells are named so imaginatively as they project to the **magnocellular** and **parvocellular** parts of the lateral geniculate nucleus, respectively.

The other two major ganglion cell classes that contribute to visual perception, comprising another fifth or so of all ganglion cells, are:

- **M ganglion cells** carry the luminance channel (L+M). They respond best to the movement of moderately large objects, receive input from all cone types, and therefore encode luminance but not color information.
- **K ganglion cells** carry the S-(L+M) channel of color information.

P, M, and K ganglion cells are most critical to visual perception. These ganglion cells project to the lateral geniculate nucleus and recipient lateral geniculate neurons in turn project to the primary visual cortex. Thus, three classes of ganglion cells carry the bulk of the retinal visual information used in *perception*.

RETINAL RECEPTIVE FIELDS ARE ORGANIZED IN A CENTER-SURROUND FASHION.

Recall from Chapter 15 that a receptive field is that part of the world where adequate stimulation elicits a response in a neuron. In the case of retinal neurons, the receptive field has a so-called “center-surround organization.” This means that a retinal neuron responds to stimulation in a central region in one way and to stimulation in a surrounding annulus, or donut, in a different way (Fig. 16-14C). For example, a retinal ganglion cell may be excited by light shining on a circular region of the retina and inhibited by light shining in the surrounding annulus. Further, retinal cells have opposing responses to light and dark stimuli. In the example above, a retinal ganglion cell excited by central light will also be excited by dark in the surround region.

Neurons in the lateral geniculate have very similar receptive field properties to those of retinal neurons. However, neurons in primary visual cortex have receptive fields that look like short slits. Different neurons respond to edges oriented at different angles. Visual areas of cortex outside of primary visual cortex are termed *extrastrate*. Extrastriate neurons have complicated receptive field properties and respond to complex stimuli such as motion in one direction but not the other, stimuli at certain depths, or even faces.

MOST TYPES OF GANGLION CELLS CONTRIBUTE TO NONPERCEPTUAL FUNCTIONS OF VISION

Retinal ganglion cells outside of the M, P, and K classes have a variety of functions. Many of them respond to overall illumination levels within large receptive fields; due to their large receptive fields, fewer ganglion cells are needed to cover the visual field and therefore these classes represent a small proportion of the total ganglion cell population, just over 10% of the total.

Most non-P, non-M, and non-K ganglion cells contribute to eye movement control. Cells that respond to changes in luminance over large regions of the visual field and to movement across the visual field project to the superior colliculus. As introduced in Chapter 11, the superior colliculus uses visual, auditory, and somatosensory input to guide orienting movements. For example, we turn to look at a chipmunk scurrying across our path. We look by turning our body and shoulders and moving our eyes. The superior colliculus is critical to all three turning movements:

1. Superior colliculus neurons *orient the body* through **tectospinal** projections to the spinal cord (see Chapter 23).
2. Superior colliculus neurons contact neurons in the vestibular nuclei, which project to the cervical cord through the **medial vestibulospinal tract** to *orient the shoulders* (see Chapter 23).
3. Superior colliculus neurons control a network of neurons that collectively control extraocular eye muscles to *orient the eyes* (see Chapter 26).

When we turn to see who walked into class late or flinch from a rapidly approaching object, we use our superior colliculus. Orienting movements mediated by retinal projections to the superior colliculus occur outside of conscious control and therefore without conscious “knowledge” of their occurrence (see Box 16-27). In other vertebrates, the superior colliculus sits at the top of the visual hierarchy but in mammals, the expanded cortex dedicated to visual processing greatly surpasses the superior colliculus in functional powers.

A new class of ganglion cells *which itself is photosensitive* was recently discovered. The photosensitivity of this class of ganglion cells stems from a pigment called **melanopsin**, which is related to the photopigment used by insects. Ambient light excites melanopsin-containing ganglion cells in a sustained manner. These **photosensitive ganglion cells** contribute to, indeed are critical for, two functions:

- Light entrainment of the circadian rhythm
- Control of the pupillary light reflex

Photosensitive ganglion cells project to the **suprachiasmatic nucleus** in the hypothalamus, a nucleus that, as its name suggests, sits just above or dorsal to the optic chiasm. Suprachiasmatic neurons coordinate circadian rhythms, so that

Box 16-27

BLindsight RESULTS FROM THE SUPERIOR COLICULUS WORKING IN THE ABSENCE OF PRIMARY VISUAL CORTEX FUNCTION.

In rare cases when all visual cortical function is impaired, a person will not have any ability to *perceive* the visual world. Yet, because the eye and its outputs are intact, an individual will have *blindsight* and will still react to visual images using the superior colliculus. Such an individual will report that they see nothing but will orient to a rapidly moving object crossing the visual field.

we are active during the day, sleep at night, release growth hormone during the night, and so on. By sensing light from the sun during the day, photosensitive ganglion cells **entrain** or align our endogenous rhythm to the Earth's circadian revolution and ensure that our internal circadian clock has a period of 24 hours. Photosensitive ganglion cells also mediate pupillary reflexes through projections to the **prectum**, a region in the rostral midbrain just ventral to the superior colliculus. Overall changes in luminance are sensed by photosensitive ganglion cells. When luminance visible to one eye increases, photosensitive ganglion cells in that eye trigger pupillary constriction in the same eye, the **direct pupillary reflex**, and in the contralateral eye, the **consensual pupillary reflex**. The prectum is a necessary way-station for pupillary reflexes, while you will remember that the Edinger-Westphal nucleus (see Chapter 12) contains the preganglionic parasympathetic neurons that control pupillary constriction.

CHANNELS OF VISUAL INFORMATION ARE PROCESSED IN PARALLEL IN VISUAL CORTEX

The tactic of splitting up the visual image into different features persists beyond the retinal ganglion cells and lateral geniculate nucleus. Primary visual cortex receives input from the lateral geniculate and processes different visual attributes in parallel, all in service of visual perception. The primary visual cortex then sends different types of information to different cortical regions, which focus on pieces of the puzzle such as color or motion. Cortical regions specialized for visual attributes can be considered intermediary within the visual hierarchy (see Box 16-28). They receive input from the primary visual cortex and send output to parietal and temporal cortical regions involved in putting the entire visual image back together again in service of the high-order goals of object recognition and movement guidance.

DORSAL AND VENTRAL STREAMS PROCESS VISUAL INPUT IN PARALLEL

After the primary visual cortex, form and color information is sent ventrally toward the temporal cortex, while motion and depth information primarily funnels into the dorsal stream bound for parietal cortex. This divergence of visual information corresponds *very broadly* to the M and P ganglion cells introduced above. The dorsal stream receives mainly M cell input with some P cell input, while information that has originated from P cells, along with some input from M cells, feeds into the ventral stream, eventually reaching the inferior temporal lobe.

The dorsal stream is very important in guiding movements, both those that we generate ourselves and those of others (see Box 16-29). For example, when we

Box 16-28

SMALL LESIONS IN MID-LEVEL VISUAL HIERARCHY LEAD TO DISCRETE DEFICITS IN PROCESSING PARTICULAR VISUAL ATTRIBUTES.

Patients with selective deficits in processing visual attributes such as color and motion are very rare, typically resulting from unusually located strokes. The inability to see colors due to a cortical lesion is termed **achromatopsia**, a disorder distinct from congenital achromatopsia, the photoreceptor-based disease discussed earlier. Patients with achromatopsia cannot recognize colors—everything looks gray to them—even though there is no damage to color processing in the retina, lateral geniculate nucleus, or primary visual cortex. Thus, achromatopsia represents a *deficit in the recognition or interpretation* of a viewed object rather than a problem with the view itself.

Patients with deficits in perceiving motion are very rare—so rare that no medical name exists for this disorder. The most famous such patient, LM,

was severely impaired by her inability to see smooth movement trajectories. In place of natural movement, LM saw objects jump unexpectedly and unpredictably from one place to another. The lips of a talking person looked like they were hopping about and liquid flowing into a container looked frozen in air. Moving cars appeared as sequential snapshots that appeared in new places unexpectedly, making it extremely tricky to distinguish the direction of traffic. As a consequence, LM experienced understanding speech, filling a measuring cup, and crossing the street as anywhere from confusing to frightening.

The rare impairments in the understanding of selective visual attributes described above provide a dramatic peek into ordinary brain processes that thankfully work so well in most of us.

see a particularly delectable piece of fruit, the dorsal part of the dorsal stream helps us understand where that fruit exists in the world and where it will be by the time we reach out to grab it. As we walk along a rocky path, the dorsal stream is critical to understanding where objects are in the world and how we can avoid stumbling on obstacles. The ventral portion of the dorsal stream is also concerned with movements but primarily in understanding others' movements. Using more ventral regions of the dorsal stream, we may grasp the trajectory of another person's swinging fist or realize that the person approaching with outstretched hand intends to shake our hand.

Box 16-29

THE DORSAL STREAM IS CRITICAL TO VISUALLY GUIDED MOVEMENTS.

The dorsal parietal cortex appears critical to spatial navigation and visually guided movements including the use of tools. Lesions in this area can cause **ideomotor apraxia**, in which individuals cannot execute certain movements such as dressing, setting the table, or cutting an apple. Patients with ideomotor apraxia have no motor deficits per se and no

sensory visual deficits. Yet, they cannot guide their movements using vision. The function of the human ventral parietal cortex and temporoparietal junction has been more controversial. This ventral part of the dorsal stream may contribute to understanding others' actions, as well as to controlling visual attention.

The ventral stream is critical to understanding that a smooth red sphere with a thin brown cylinder coming out of the indented top is an apple. In other words, we recognize what optical images represent using the ventral stream (see Box 16-30). Of particular interest is the fusiform face area, a discrete region within the inferotemporal cortex that specializes in recognizing faces, both generically and individually. Thus, the fusiform face area is responsible for recognizing any face as a face and also for identifying individual faces.

WE NEED TO PAY ATTENTION IN ORDER TO SEE

Optical input washes over us unless we attend to what we are looking at. Every day we blink thousands of times and yet we do not perceive the back of our eyelids . . . until now that I have called attention to the blank scene accompanying each blink. It is commonplace that we fail to notice a friend's new hairdo or glasses. Our poor *attention* to visual scenes is central to our abysmal reliability as eyewitnesses. However, when we pay attention to what we are seeing and practice attentive viewing, we can quickly become experts at seeing details and objects. This is the central theme in the child's game of "Where's Waldo?" As we find Waldo in one, two, and then three scenes, we become expert at finding the

Box 16-30

LESIONS IN THE VENTRAL STREAM IMPAIR THE RECOGNITION OF VISUAL OBJECTS.

Damage to the ventral stream, particularly the inferotemporal cortex, impairs the recognition and interpretation of visual images, a condition termed *visual agnosia*. Agnosia refers to a class of disorders in which objects cannot be recognized or interpreted using a particular sense—in this case vision—although no deficit exists in the sensory pathways. Thus, there is nothing wrong with a patient's eye, retina, lateral geniculate nucleus, or primary visual cortex, and the input to the ventral stream is normal. Nonetheless, patients with visual agnosia experience difficulty in identifying objects using sight even while retaining the ability to identify the same objects using other senses. As described in Chapter 1, Oliver Sacks' patient, Dr. P., could not identify a rose by looking at it but immediately recognized the rose by smell.

Visual agnosia is a heterogeneous group of disorders. Some patients show deficits in recognizing

all objects, others in recognizing a subset of objects, such as tools. In the latter category, **prosopagnosia** is a particularly intriguing disorder involving the failure to recognize faces. Some **prosopagnostic** patients recognize no faces, including their own, and in fact do not know that they are looking at a face. Other patients may know that they are looking at a face but cannot identify the individual, even when that individual is a family member. Still other prosopagnostic patients may recognize faces but cannot interpret expressive social cues.

In sum, prosopagnosia and the other visual agnosias provide a compelling glimpse into the biological categorization of visual objects, a categorization often obscured by classification systems imposed by dominant cultural norms.

PATIENTS WITH NEGLECT DO NOT RECOGNIZE THE LEFT SIDE OF THE WORLD.

Hemispatial neglect is a bizarre syndrome that results from right hemispheric damage, typically in the ventral parietal lobe just caudal to the somatosensory strip. *The left half of the world simply does not register for patients with neglect.* Patients may get into car accidents with the left side of their car without recognizing it. For example, the late journalist Robert Novak ran into a pedestrian, presumably approaching from the left side, and did not stop. Only blocks later, when confronted by a bicyclist approaching from the right did Mr. Novak stop. Days after this incident, it was announced that Mr. Novak had a brain tumor in the right parietal lobe. Mr. Novak died a little over a year later. There is no treatment for neglect per se. Rather patients with neglect are treated for the underlying cause—usually a tumor, as in Mr. Novak's case, or a stroke.

red-and-white striped shirt, blue pants, and floppy hat associated with Waldo. We then start to find Waldo more quickly. In a similar way, we can become expert in visually recognizing, even after only a brief glance, classmates, fossils, birds, airplanes, trees, cars, and so on.

The parietal cortex controls the application of attention to the outside world. Attention is **multimodal**, meaning that it uses visual, auditory, and somatosensory information, and in fact all sensory input. Curiously, the parietal cortex controls attention asymmetrically. Lesions in the right parietal cortex, typically ventral parietal and temporoparietal regions, can result in the loss of, or complete failure to recognize, the left side of the world (see Box 16-31). The prevailing view is that the right parietal cortex is responsible for applying attention to both left and right parts of the world, whereas the left parietal cortex preferentially applies attention to the right part of the world. Neglect reminds us in dramatic fashion that vision is not passive but requires active engagement and attention for full appreciation, recognition, and understanding of the visual world.

WE LEARN TO SEE BY VIEWING THE WORLD IN FOCUS

Our ability to interpret points of light, photon-hits distributed over the retina, as objects and color and motion and the impetus to move is **learned**. To learn the trick of converting optical source code into interpretable information we need practice, lots of practice. As babies, we open our eyes upon awakening and start practicing. We move our hand in front of our face and learn how the hand image corresponds to the hand trajectory. Through infancy, the experiment of vision continues day in and day out, with the trial-and-error interpretation of millions of snapshots and movies. Now imagine that, during the practice years, our optical image is obscured, blurred, stretched, or somehow not in correspondence with the physical world. In this case, the daily visual experiments of infancy “won’t work.” If there is no rhyme or reason to the relationship between the optical image and the tangible world, the brain cannot set up the correct neural circuits to allow for interpretation of new incoming optical images. A person who grows up in a figurative “visual fun house,” where images are randomly and unpredictably stretched this way or that, cannot learn the rules that transform photic input into accurate mental images. Therefore, even if this person is placed as an adult into a normal environment and has perfect refractive correction, so that images form crisply on the retina, the *brain lacks the capacity, circuits fine-tuned through visual experience, to interpret optical images*. Thus, this person will be functionally blind or at least severely visually impaired (see Box 16-32).

Not only does vision depend on normal development but also on development that occurs during a **critical period** of an individual’s life. The critical period is a developmental phase that favors *facile* learning of a given natural process. In humans, the critical period for vision is thought to be the first 4 years or so of life. Significant learning also occurs outside of the critical period but occurs optimally

DEVELOPMENTAL DISRUPTION OF VISION CAUSES PERMANENT, SEVERE, AND LARGELY UNTREATABLE VISUAL IMPAIRMENT.

Impaired vision during the visual critical period permanently damages visual acuity and eye movements. People with congenital cataracts that are not corrected early in life fail to develop normal vision even if those cataracts are later removed. Strabismus—recall that this refers to any misalignment of the eyes—also prevents normal development of visual function. The impairment of adult vision solely as a result of abnormal development is a condition termed **amblyopia**. This means that the *impaired vision is a consequence of abnormal development and persists even if the original optical problem is resolved*. The most common form of amblyopia

results from **anisometropia**, a condition in which the eyes have different refractive errors, due to different eye lengths. Anisometropia causes babies to see different images in the two eyes. Thus, the cortex “sees” unmatched, unaligned images, and cortical circuits do not develop correctly. Whenever visual development is impaired, visual acuity is greatly reduced, particularly at high spatial frequencies. Further, one may imagine that it would be difficult to learn where to look if the world is too blurry. Indeed, eye movements are abnormal in people whose vision is impaired during the critical period, a time when eye movement circuits are also developing.

and most effortlessly during the critical period. Another example of a critical period is learning a language, which is easiest before the age of 3. Language learning becomes progressively more difficult, albeit not impossible, to learn as a person ages. Although individual differences are commonplace in language-learning abilities, *all* of us learned a language as babies without study or effort, and none of us adults could learn a new language without both study and effort. Similarly, we *learn* the language of visual perception as babies.

The story of Mike May dramatically highlights the importance of learning to see at a young age. May was blinded by corneal scarification caused by a chemical accident at the age of 3. More than four decades later, May received a corneal transplant, making his eye patent to light again and opening the possibility of vision. At the time of May’s accident at age 3, circuits supporting color and motion vision were more developed than were those for form vision. Therefore, May immediately recognized colors and correctly remembered the color names, names that he had learned before his accident. May discovered that he could kick and catch a moving ball, visually guided movements, without effort. Yet, even years after corrective surgery, May’s form vision is sketchy. May can read 1-inch-high letters that are about 6 inches, about 15 centimeters, away. He can see forms like the moon, buildings, shadows, signs, and people. However, he has difficulty interpreting the forms. Cracks in the sidewalk, steps, and curbs form images that May uses cognitive tricks to interpret. He has learned tricks to tell women from men and to recognize individuals, including family members, from the appearance of their faces. May’s story provides a fascinating window into vision, into all the visual knowledge that we employ to accomplish seeing.



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CHAPTER 17

AUDITION: COMMUNICATION PORTAL

HEARING IS THE MAJOR HUMAN PORTAL FOR INTERPERSONAL COMMUNICATION

We care a great deal about hearing because most of us communicate through spoken language. Deafness or hearing loss acquired during adulthood profoundly reduces quality of life by severely impacting communication with others (see Box 17-1). In such circumstances, the most devastating part of hearing loss or deafness is the social isolation that results. Babies who are deaf at birth or lose their hearing during infancy and who learn to communicate either orally or by sign language, suffer less from social isolation. A residual problem for deaf individuals, regardless of history, is the inability to overhear conversations as well as meaningful sounds, such as approaching vehicles, which warn of impending dangers.

HEARING REQUIRES CONDUCTION OF AUDITORY INPUT TO THE COCHLEA FOLLOWED BY SENSORINEURAL PROCESSING

There are three fundamental steps involved in hearing:

1. **Conduction** refers to the ushering of airborne sounds into the inner ear. As sound travels through the external and middle ear, the intensity of the sound decreases, but not by as much as would occur without the *amplification* accomplished within the external and middle ear. This amplification is passive or mechanical, dependent solely on the physical properties of the external and middle ear. The ultimate result of conduction is that airborne

THE IMPACT OF HEARING LOSS ON A PERSON'S LIFE VARIES WIDELY.

There is no uniform or even predominant reaction to hearing loss or deafness. In part, this heterogeneity of reactions is due to the wide variety of personal histories and circumstances associated with the loss. Individuals who are born deaf have a very different experience from those who lose some or all of their hearing during adulthood. Likewise, the experience of growing up deaf within a deaf community clearly differs from growing up deaf in the hearing world. The experience of significant but not total hearing loss late in life is different yet. Like the differences in experiences, there are huge differences in how affected individuals cope with the inherent challenges of living with hearing loss or deafness. A number of superbly written memoirs are worthwhile reading for anyone interested in understanding

the varied effects of hearing impairments on human lives:

- Chorost, M. *Rebuilt: My journey back to the hearing world*. Boston, Houghton Mifflin, 2005.
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sound is transformed into a pressure wave within the fluid-filled spaces of the cochlea.

2. *Peripheral sensorineural* transduction and processing includes an active amplification step called *cochlear amplification*, followed by transduction by cochlear hair cells. Hair cells transmit information to spiral ganglion cells across a synapse. The ultimate output from the spiral ganglion cells consists of trains of action potentials. The axons of spiral ganglion cells travel through the vestibulocochlear nerve to serve as the afferents to the central nervous system (CNS).
3. Central processing of cochlear input lets us know the location of sound sources. More important to the human experience, the CNS allows us to interpret meaning from acoustic sounds, including speech. In this chapter, we focus on the latter process.

Hearing problems including both deafness and hard of hearing conditions invariably result from an impairment of either conduction or sensorineuronal processing (see Box 17-2).

Within the periphery, the first step in audition is to capture airborne sounds and to transform those sounds into fluid pressure waves. The external and middle ear (Fig. 17-2) are responsible for the capture, conduction, and air-to-fluid transformation of sound. As sound travels through the external ear, its intensity increases. This amplification step is necessary because almost half of the sound intensity that arrives at the *tympanic membrane*, the border between the external and middle ear that is

HEARING LOSS IS CLASSIFIED INTO TWO MAJOR CATEGORIES.

The classification of hearing loss reflects the division of labor between the external and middle ear on one hand and the inner ear on the other. *Both hearing loss and deafness are caused by peripheral lesions of the external, middle, or inner ear and not by central nervous system lesions.* External and middle ear deficits lead to **conduction hearing loss**, whereas problems with hair cells, spiral ganglion afferents, or their connection produce **sensorineural hearing loss**. We can distinguish conduction from sensorineural hearing loss by the use of two tests easily performed with a tuning fork (Table 17-1).

In the **Rinne test**, a person is asked to compare the loudness of a vibrating tuning fork placed just outside the ear versus when the tuning fork is placed on the bone just behind the ear (Fig. 17-1). The tuning fork placed outside the ear produces an airborne sound that reaches the cochlea through the normal channel of air conduction. The tuning fork placed on the bone beside the ear produces a sound that is conducted through bone to the cochlea. Because of the amplification provided by the external and middle ears (see text), sound arriving via air is perceived as louder than the same sound arriving by bone conduction. Therefore, a person with normal hearing will perceive the air-conducted sound to be louder than the bone-conducted sound. In contrast, vibrations from a tuning fork placed on the skull behind the ear bypass the external and middle ear to reach the cochlea directly through bone conduction. Therefore, a person with conductive hearing loss, due to a problem in the external or middle ear, will perceive bone-conducted sound to be louder than the air-conducted sound. A person with sensorineural hearing loss will resemble a person with normal hearing in that airborne sound is perceived as louder than bone-conducted sound. Sensorineural hearing loss decreases the perceived loudness of all sounds on the affected side or sides, but these deficits are not detected by the Rinne test.

The **Weber test** is performed by placing a vibrating tuning fork on the vertex of the head. Normally, we hear the sound of the tuning fork as equally loud on either side. In an individual with sensorineural hearing loss, the perceived sound is, of course, greater on the unaffected side. In an individual with conduction hearing loss, the perceived sound is greater on the *affected* side. Although still

somewhat mysterious, one explanation for this latter result is that an individual with conductive hearing loss hears only the bone-conducted sound produced by the tuning fork and does not hear any background sounds—traffic, people talking, birds singing, and so on—that are conducted through the external and middle ear. Because there is no background level of stimulation, the perceived sound of the vibrating tuning fork on the vertex of the head will be greater on the side affected by conductive hearing loss (Weber's law, see Chapter 15).

The Rinne and Weber tests can only detect sensorineural hearing loss that is unilateral, or at least more profound on one side than the other. To identify bilateral hearing loss, as occurs often in age-related hearing loss and several other conditions, an audiological examination is needed. In an audiological examination, the intensity threshold for detection of sounds at different frequencies, spanning across audible frequencies, is measured in a controlled environment.

The treatment options for conductive and sensorineural hearing loss are quite different. In general, practical solutions or surgical remedies exist for many forms of conductive hearing loss. In contrast, the strategy used for sensorineural hearing loss is to boost the input signal intensity by use of a **hearing aid**. When complete or virtually so, hearing loss is termed *deafness*. In many cases, deafness stems from one of a large variety of genetic conditions that render the hair cells inoperative. The only therapeutic option available to provide aural sensitivity to deaf individuals is a **cochlear implant** (see Box 17-9). Note that patients need to have a working vestibulocochlear nerve in order to be eligible for a cochlear implant. The function of a cochlear implant replaces that of the peripheral sensorineural apparatus, taking the place of both the hair cell and the hair cell-to-spiral ganglion cell synapse.

Sign language or oral language—speech and lip-reading—can allow deaf people to communicate and lessen the social isolation ordinarily associated with hearing loss. Learning either sign language or oralism is a more viable option for children, either children born deaf or those deafened in their early youth, than for individuals who are deafened as adults.

TABLE 17-1. THE RINNE AND WEBER TESTS PROVIDE A QUICK METHOD FOR DETECTING UNILATERAL CONDUCTIVE OR SENSORINEURAL HEARING LOSS

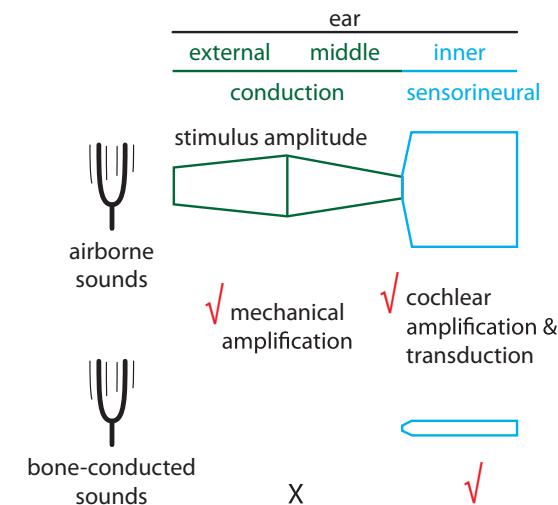
CONDITION	RESULT OF RINNE TEST	RESULT OF WEBER TEST
Normal	Airborne louder than bone for each ear	Loudness is equal on left and right
Unilateral conduction hearing loss	Bone louder than airborne	Louder on affected side
Bilateral conduction hearing loss	Bone louder than airborne for each ear	Loudness is equal on left and right
Unilateral sensorineural hearing loss	Airborne louder than bone for each ear	Louder on unaffected side
Bilateral sensorineural hearing loss	Airborne louder than bone for each ear	Loudness is equal on left and right

Both tests require only a tuning fork. The Rinne test is used to diagnose or rule out a conductive hearing loss. A vibrating tuning fork is placed in the air, just beside the ear, or on the bone behind the ear. The patient is asked which location produces a louder sound. In the absence of the amplification provided by conduction through the external and middle ear, airborne sounds are perceived as softer than bone-conducted sounds. A person with conductive hearing loss will therefore report that the bone-conducted sound is louder than the airborne sound. Another method is to keep the vibrating tuning fork on the mastoid until it can no longer be heard. When it can no longer be heard through bone conduction, the tuning fork is moved to a point in the air outside the ear. A person with normal hearing, or a mild sensorineural hearing loss, will hear the airborne sound. The Rinne test should be performed on each ear.

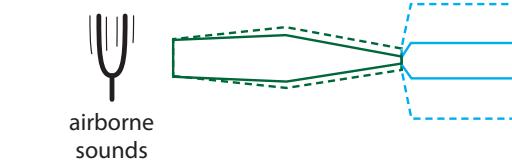
The Weber test involves placing a vibrating tuning fork at the vertex of the head. This should produce a sound that is perceived as equally loud on the two sides. However, an individual with unilateral conductive hearing loss will perceive the sound as louder on the affected side while an individual with unilateral sensorineural hearing loss will perceive the sound as louder on the unaffected side. Note that neither the Rinne nor the Weber test can distinguish bilateral sensorineural hearing loss from normal hearing.

Figure 17-1. A: Airborne and bone-conducted sounds are processed differently by the ear. In this diagram, the amplitude of the stimulus is denoted by the height of the polygons. Airborne sounds are amplified by passing through the external and middle ear. These sounds arrive at the inner ear as pressure waves within the cochlea. Within the inner ear, an active process, cochlear amplification, further amplifies the pressure wave, which is then transduced into a graded potential in the hair cell. The final step of sensorineural processing within the inner ear is the synaptic transmission from the hair cell to spiral ganglion cells. Bone-conducted sounds reach the inner ear directly, without passing through the external and middle ears. Although cochlear amplification, transduction and synaptic transmission all still occur, the starting stimulus is small because it has not been amplified by normal conduction. **B:** Conduction hearing loss occurs for a variety of reasons, including impacted ear wax or a punctured ear drum. As a result the stimulus delivered to the inner ear is smaller in magnitude (solid lines) than what would be delivered if conduction were normal (dotted lines). The consequence is that the ultimate effect of cochlear amplification is correspondingly reduced. There are practical or surgical solutions for most types of conduction hearing loss. **C:** The predominant type of age-related hearing loss is due to a loss of cochlear amplification (top panel) with the external and middle ear, as well as the transduction process, working normally. When cochlear amplification is diminished or even abolished, the result is a profound hearing loss. This type of hearing loss is typically treated with a *hearing aid*, which boosts the conduction amplification prior to the inner ear. The delivery of a larger stimulus to the inner ear mitigates the loss of cochlear amplification but does not replace it. Most congenital forms of deafness occur because of a deficit in either transduction or synaptic transmission (x in bottom panel). The only treatment for this type of sensorineural deafness is a cochlear implant.

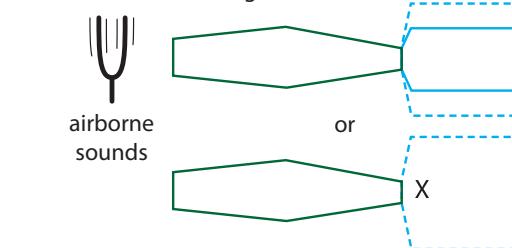
A. Airborne vs bone conduction



B. Conduction hearing loss



C. Sensorineural hearing loss



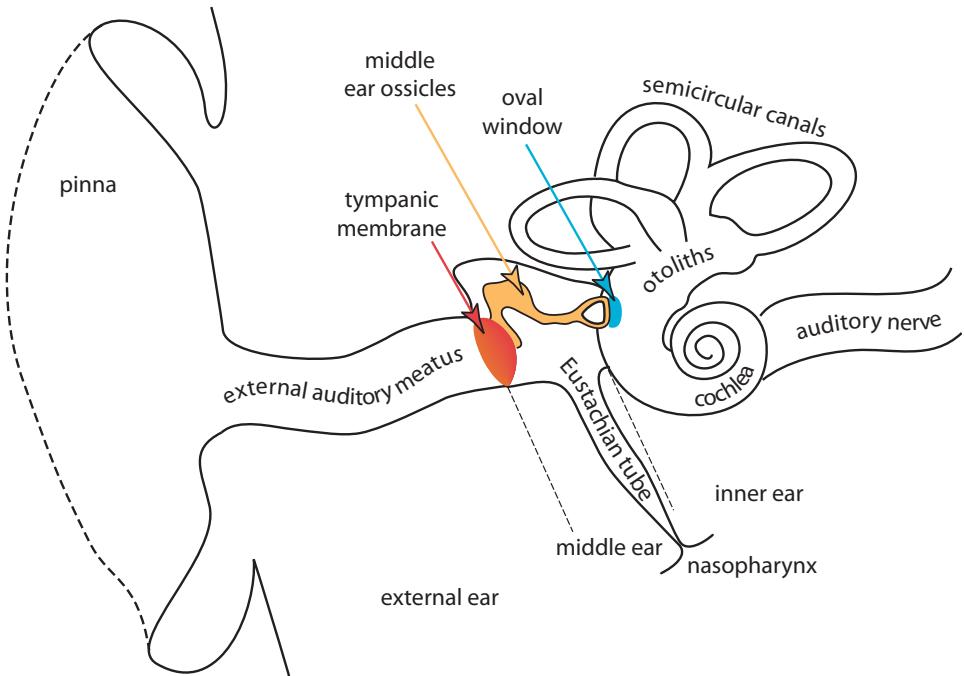


Figure 17-2. The ear is divided into external, middle, and inner compartments. The external ear includes the pinna and the external auditory meatus or ear canal. The tympanic membrane forms the border between the external and middle ears. The middle ear is a closed chamber with only one way out, the Eustachian tube. At rest, the Eustachian tube is closed at the pharyngeal end. The middle ear ossicles (shown altogether in ochre) physically convey vibrations of the tympanic membrane to the inner ear via the oval window. The oval window opens onto the fluid-filled bony labyrinth, which includes both the hearing and vestibular sensory apparatus. The cochlea contains the hair cells that support hearing, whereas vestibular hair cells are contained in the semicircular canals and otoconial organs (see Chapter 19). The auditory nerve contains the axons of spiral ganglion cells that carry cochlear input into the central nervous system. The spiral ganglion cells are located within the cochlea itself (not shown).

commonly referred to as the ear drum, does not make it through to the cochlea. Airborne pressure waves move the tympanic membrane, which in turn moves a series of **ossicles**, the tiny bones in the middle ear. Movement of the chain of ossicles results in the **stapes**, the final ossicle in the chain, beating upon the **oval window** of the fluid-filled cochlea within the inner ear (Fig. 17-2). Because of this arrangement, about 60% of the sound energy that reaches the tympanic membrane makes it through to the cochlea.

Within the cochlea, several important steps occur. First, sound at different frequencies is distributed in the form of waves of fluid pressure to different parts of the cochlea. This distribution is the basis for the gross tonotopy of the cochlea. Sensory cells in the cochlea itself then amplify pressure waves of different frequencies to fine-tune the tonotopic map. The pressure waves move the **stereocilia** of the hair cells, the stimulus for sensory transduction. Graded potentials in hair cells lead to a change in the amount of neurotransmitter released from the hair cell onto spiral ganglion afferents. Finally, spiral ganglion cells carry sound information from the cochlea to the cochlear nuclei that cap the restiform body in the rostral medulla.

Within the nervous system, auditory information from the two ears is combined almost immediately (see Fig. 12-7). As a result, central auditory pathways above the cochlear nuclei carry redundant auditory information. Consequently, lesions within the brainstem and thalamus do not produce symptomatic difficulties for humans.

Therefore, we describe ear function in some detail and then skip from the auditory nerve to cortex to consider how we make sense of the sounds that we hear and to consider in particular how we both produce and understand speech.

SOUNDS RANGE FROM PURE TONES TO NOISE

Sound consists of pressure waves. The pressure must act on something to produce a sound; there is no sound in a vacuum. In the case of airborne sounds, sound acts on the molecules of the atmosphere. Sound produces alternately **compression**, an increase in pressure and **rarefaction**, a reduction in pressure.

Box 17-3

THE FREQUENCY AND AMPLITUDE OF SOUND WAVES LARGELY DETERMINE PITCH AND LOUDNESS.

Recall from Chapter 15 that visual, auditory, vestibular, and mechanical stimuli can be broken down into component sine waves, sometimes a few, and more typically, a great number. Sound waves dominated by a periodic component are perceived as a **tone**. Tones are accompanied by harmonics that consist of sounds at integer multiples of the fundamental frequency (Fig. 17-3A). For example, middle C in Western music has a frequency of about 261 Hz. Therefore, when a person plays middle C on a piano, the sound that results has power at frequencies of 523 (=1st harmonic = $2 * 261$), 785 (=2nd harmonic = $3 * 261$), 1,047 (=3rd harmonic = $4 * 261$), and so on as well as at 261 Hz.

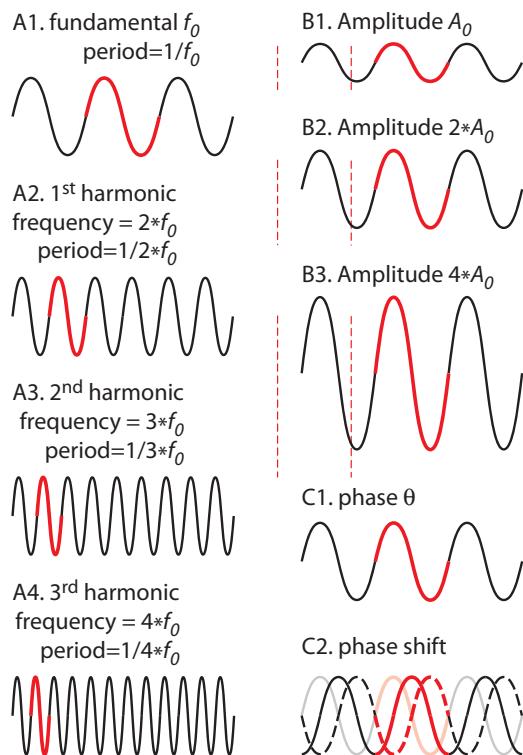
The lowest frequency with power is called the **fundamental frequency** and is typically perceived as the **pitch** of the sound. Although perceived pitch increases as fundamental frequency increases and decreases as fundamental frequency decreases, pitch is influenced by other features of an incident sound beyond simply the fundamental frequency. Auditory illusions take advantage of the additional influences on pitch perception. For instance, a sound that has power at 523, 785, 1,047, and so on will be perceived as a middle C even if the fundamental frequency of middle C, 261 Hz, is not present at all in the acoustic stimulus. Nonacoustic factors can also influence our perception of pitch. The loudness of a sound is related to the amplitude of the sound wave (Fig. 17-3B).

Pitch and loudness are not enough to describe the rich variety of sounds that we perceive. An additional aspect of sound is **timbre**. Because of a difference in the sound envelope, the middle C produced by a guitar, an oboe, and a human voice are distinguishable. The distinction of sounds with different timbres but the same fundamental frequency depends on three factors:

- The frequencies present: The number of harmonics present and the power in each of these harmonics varies across sounds with different timbres. In addition to variation in the harmonics, there may be **inharmonics**, frequencies that are noninteger multiples of the fundamental frequency.
- The envelope waveform: The form of the sound envelope, including the rise and decay times of a sound, differs across sounds with different timbres.
- Vibrato: Natural sounds such as the human voice have a modulated or changing fundamental frequency. The fundamental frequency of rudimentary synthetic voices is constant rather than modulated and therefore can be instantly identified as “artificial.”

In contrast to tonal sounds, white noise has power at many frequencies, with no one frequency having significantly more power than the rest.

Figure 17-3. A: The frequency of a sound is a major influence upon the perceived pitch. A pure tone, such as middle C, has a fundamental frequency (f_0), the number of cycles per second. The period (red region) of a sinusoidal wave is the reciprocal of the fundamental frequency ($1/f_0$). Harmonics of a tone are tones at frequencies that are integral multiples of the fundamental frequency. The first harmonic (A₂) is a sinusoidal wave with double the frequency and half the period, the second harmonic (A₃) is a sinusoidal wave with triple the frequency and a third of the period, and so on. B: The amplitude of a sound wave is a major influence upon the perception of loudness. Amplitude can increase (B₁–B₃) without affecting the period (shown in red) or frequency. C: Phase refers to the starting point of a sinusoidal wave. A shift in phase is equivalent to a shift in time. Because of the time needed for transduction and synaptic transmission, the responses of hair cells and spiral ganglion cells to a sound are phase-shifted from the time of sound onset. Phase shifts are typically described by an angle, θ , which can vary from zero to 2π , a full cycle. Phase shifts of a quarter cycle or $\pi/2$ (solid line) and a half cycle or π (dashed line) from the original phase (dim line) are shown in C₂.



As with visual and mechanical stimuli, sounds can be broken down into component sine waves. A sound with one predominant frequency produces a sound that we perceive as a pure tone at a given **pitch** (Box 17-3). As adults, we hear sounds that range in frequency from 20 to about 16,000 Hz or cycles per second (see Box 17-4). Sounds without a dominant frequency sound are termed noise.

Box 17-4

WE LOSE HEARING AT THE HIGHEST FREQUENCIES IN OUR FIRST THREE DECADES OF LIFE.

Speech involves frequencies that range from about 400 Hz to 8,000 Hz (or 8 kHz). Musical instruments produce sounds as deep as 8 Hz, the lowest note produced by an organ, or 65 Hz, the lowest note produced by a cello. At the high end, the highest note sung by a soprano is more than 1 kHz, the highest note of a flute more than 2 kHz, and the highest note of a violin more than 4 kHz. When we are born, we can hear frequencies up to 20 kHz or so, but we lose the ability to hear the highest frequencies as we age. By the time we are in our twenties, most of us only hear frequencies up to 16 kHz or so. This loss of sensitivity has been exploited

both by the young and the old. Young people use ringtones at frequencies above 16 kHz to allow them to receive cell phone calls unnoticed by their teachers, who are typically unable to hear the high-frequency sounds. Conversely, business owners have employed devices that emit a high-pitched sound, at about 17 kHz, designed to discourage young people from hanging around outside stores. The high pitch can be heard by young people and produces a bothersome effect. The shop-owners, as well as their desirable customers, presumably over 20–25 years of age, fail to detect or be bothered by the sound.

Our auditory system is extremely sensitive. In fact, we would hear blood whooshing through capillaries if they were nearby. As it turns out, the capillaries supplying the inner ear are located far enough away from the hair cells that we do not hear blood flowing within. Our ability to “hear the ocean in a seashell” is in fact due to the extreme sensitivity of our auditory system. You can imitate this by simply cupping your hand or a large glass over your ears. The whoosh that you hear is your perception of the resonating motion of air molecules.

THE EXTERNAL EAR FUNNELS AND AMPLIFIES SOUNDS

The outer ear or **pinna** collects sound and funnels it into the **external auditory meatus** (Fig. 17-2). In an analogous way to an organ pipe or a flute, the external auditory meatus acts as a *resonance tube*, meaning that sound waves bounce back and forth in the canal and summate. The result is that the amplitude of sound waves increases by 5–10 dB (see Box 17-5). To appreciate the acoustic amplification provided by a tube, hold a toilet paper roll up to your ear. In a quiet room, you will hear very little without the tube but will discern a definite sound with the tube placed against your ear. The resonating frequency depends on the width and length of the tube. The human auditory canal is such that frequencies of 2,000 to 5,500 Hz, the core frequency range of human speech (see below), resonate within the canal. This means that the loudness of sound waves with frequencies of 2,000–5,500 Hz increases by 5–10 dB. Of course, earwax can greatly impair hearing as sound can only pass through an unobstructed canal (see Box 17-6).

Box 17-5

DECIBELS ARE A RELATIVE MEASURE OF SOUND PRESSURE.

The **bel** is a term, named after Alexander Graham Bell, which describes the relative amplitude, or loudness, of one sound in comparison to a standard sound. The bel is an enormous unit and is virtually never used. Instead we talk of **decibels**, which are tenths of bels and are abbreviated as **dB**. Decibels are typically computed for sound pressure as:

$$dB = 20 \log \frac{P_1}{P_0}$$

where P_1 is the sound whose loudness is being measured and P_0 is the standard sound pressure. The standard sound pressure is that of a just-detectable sound. Thus, a sound that exerts ten times the sound pressure at the human threshold for sound will be a 20 dB sound. The range of sound intensities

in modern life extends from less than 10 dB—the soft breathing of a sleeping infant—to 130 dB or more—a nearby siren. The loudness of a sound decreases as one moves away from the sound source and as obstacles are interposed between the sound source and the ear. A jet engine located a football field away produces a roughly 150 dB sound but when aloft at 30,000 feet, or about 9,000 meters, the same engine sounds far less loud. Similarly, very close to a jackhammer, sound levels are greater than 100 dB but are greatly reduced by simply covering the ears. Hearing damage can occur with long-term exposure to sounds as soft as 80 dB and more rapidly upon exposure to sounds of ≥ 120 dB, levels reached at some live music performances, as well as at some construction sites.

CERUMEN IS A COMMON REASON FOR HEARING IMPAIRMENT IN ADULTS.

Earwax or **cerumen** is naturally made by sebaceous glands lining the ear canal. Although cerumen has the positive effect of lubricating the external auditory meatus, it can impair hearing if it accumulates and becomes impacted. Impacted cerumen occurs fairly commonly, particularly among nursing home residents and intellectually disabled individuals who may not adequately care for themselves. Impaired hearing due to impacted cerumen decreases social communication and can therefore

cause great distress to individuals, particularly those in vulnerable populations.

Removal of impacted cerumen is accomplished mechanically using some kind of manual scoop or by irrigation with saline or a **ceruminolytic**, a compound that breaks down cerumen. Although aggressive treatment of impacted cerumen is warranted, care should be taken as treatment options can produce several potential complications, such as perforation of the tympanic membrane.

The external auditory meatus ends in the conically shaped **tympanic membrane** or eardrum. Sounds that enter the ear canal cause pressure waves of the tympanic membrane. As a result, the membrane oscillates back and forth at the frequency of the incident sound wave. The tympanic membrane is the bridge between the external ear and the middle ear.

THE MIDDLE EAR TRANSFERS ENERGY FROM AIR TO THE FLUID-FILLED INNER EAR

The middle ear is a closed bony chamber with one outlet, the Eustachian tube (Fig. 17-2), that leads to the throat (see Box 17-7). The middle ear forms the bridge between the external ear and the cochlea within the inner ear (Fig. 17-4). On the external ear side is the tympanic membrane, and on the inner ear side is the **oval window**, the input portal to the cochlea.

Sounds that we hear arrive through the *air* at the external ear, but the cochlea where sensory transduction occurs is a *fluid-filled* structure. When sound waves traveling through air hit water, they are reflected back into the air, and for the most part, do not enter water. Indeed, when we put our head under water, we are deaf to even the loudest airborne shouts. The middle ear addresses this problem. Airborne sound waves move the tympanic membrane, which moves the middle ear ossicles, and the latter movement sets up fluid movements in the inner ear. Consequently, we lose less than half of the energy contained within incident sound when that sound transfers through the middle ear: about 40% of the sound energy present at the tympanic membrane is lost at the level of the cochlea. Even so, a 40% loss is a vast improvement over the roughly 99% loss of sound energy that occurs when airborne sound encounters water directly.

As mentioned above, tiny bones called ossicles are present in the middle ear. The three ossicles are, from outside to inside, the **malleus**, **incus**, and **stapes** (Fig. 17-4A).

THE EUSTACHIAN TUBE IS THE ONLY POTENTIAL OUTLET FROM THE MIDDLE EAR.

The Eustachian tube runs from the middle ear to the pharynx, or upper throat. On the pharyngeal side, the Eustachian tube normally sits in a closed position (Fig. 17-2). During swallowing, pharyngeal muscles pull on and then elevate the soft palate and in so doing, pump the contents of the tube. Opening and closing the mouth using large jaw movements can approximate the effect of swallowing. In either case, the Eustachian tube is not opened in the sense that it affords free passage from the middle ear to the throat all at once. Rather, swallowing propels the tubular contents, both gaseous and fluid, through the tube, in both directions. After enough iterations, this action allows equilibration between the pressure and contents within the middle ear and within the pharynx. Pharyngeal pressure is equivalent to atmospheric pressure. Thus, when descending rapidly from a higher to a lower altitude, as during an airplane landing or an elevator descent, the pressure in the middle ear is lower than the atmospheric pressure of the lower altitude. To equilibrate these pressures, we chew gum or repeatedly open and close our mouth.

In an upright adult, the middle ear is located just above the pharyngeal exit point of the Eustachian tube whereas in a supine person, the reverse is true. This means that normally as we move around, fluid accumulated in the middle ear drains through the Eustachian tube and exits into the throat during swallowing. Certain conditions hamper the drainage of middle ear fluid. Some people simply have a congenitally narrow Eustachian tube. In individuals born with a **cleft palate**, the insertions of the muscles surrounding the Eustachian tube are changed in such a

way that greatly hinders or prevents *milking*, meaning pumping, of the Eustachian tube contents. When mucus cannot be drained, infections in the middle ear, termed **otitis media**, worsen and in the most severe instances, can cause rupture of the tympanic membrane. The middle ear and the tympanic membrane receive a dense innervation from nociceptors and consequently, middle ear infections are painful, sometimes severely so. Although the tympanic membrane often regrows spontaneously, it sometimes fails to do so; in such cases, surgical reconstruction, a **tympanoplasty**, can be used to restore function.

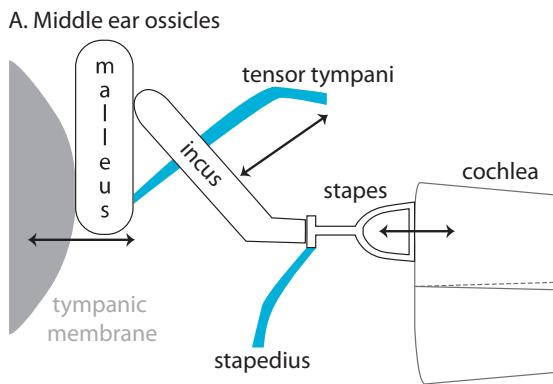
In infants and children, the muscles that surround the Eustachian tube compress the tube but in adults, these same muscles are stretched away from the tube. This difference in muscle anatomy combined with a shallower tube trajectory in children renders drainage from the middle ear more difficult in children than in adults. Therefore, early in the course of a respiratory infection, mucus may move from the pharynx to the middle ear chamber, particularly when an individual is supine, as during sleep. Eventually, inflammation associated with infections can keep the Eustachian tube closed at the pharyngeal end.

The anatomical features of the Eustachian tube peculiar to infants, combined with an inability to be instructed on how to swallow, cause prelingual infants to have a very difficult time equilibrating pressure in the pharynx and middle ear. The discomfort resulting from unequal pressures is likely a major reason why babies and infants cry during airplane rides, particularly during takeoffs and landings.

The malleus attaches to the internal surface of the tympanic membrane on one side and to the incus on the other. The incus attaches to the stapes, the innermost middle ear bone. The stapes moves the oval window of the cochlea back and forth. The ossicles in the middle ear are so light that vibrations of the tympanic membrane are enough to move them. The pathological attachment of the stapes to the temporal bone results in conductive hearing loss (see Box 17-8).

The physical arrangement of the three ossicles amplifies sound pressure through two mechanisms. First and most influential, the area of the tympanic membrane is roughly 15 times greater than the contact area between the stapes and the oval window (Fig. 17-4B). Since the entire force of the sound on the ear drum is focused onto the small stapes, the pressure, force per unit area, is amplified by about 15 times.

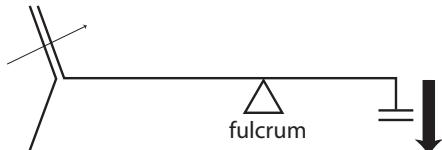
Figure 17-4. A: The three ossicles of the middle ear form a physical link between the tympanic membrane and the cochlea. The malleus attaches to the back of the tympanic membrane and to the incus on the other side. The incus then attaches to the stapes, which pushes on the oval window of the cochlea. The two middle ear muscles (blue), the tensor tympani, and the stapedius, attach to the malleus and the head of the stapes, respectively. B: Most of the amplification achieved by the middle ear results from the transfer of the force exerted on the large tympanic membrane onto the far smaller oval window. The increase in sound pressure, proportional to the width of the arrows, is about 16 times greater on the oval window than on the tympanic membrane. C: The ossicles are arranged like a lever, with the fulcrum closer to the oval window than to the tympanic membrane. The result of this is a further amplification in sound, by a factor of about 1.3, along with a decrease in displacement, signified by the length of the arrows. Thus, small forces upon the tympanic membrane are transformed into larger forces exerted over a smaller distance at the oval window. D: When the tensor tympani contracts, it pulls the malleus and stretches the tympanic membrane. Stretching the tympanic membrane results in lower-amplitude and higher-frequency vibrations of the ear drum in response to any given displacement. Contraction of the stapedius pulls the stapes away from the oval window, so that the force of pressure waves communicated by the stapes to the cochlea is reduced. Activation of stapedius and tensor tympani muscles greatly decreases the pressure exerted upon the oval window.



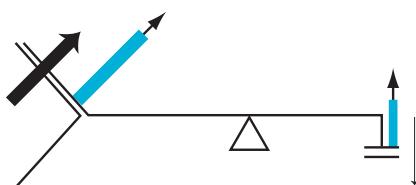
B. Amplification due to reduction in surface area



C. Total middle ear amplification



D. Amplification with middle ear muscle activation



The mechanical advantage of the decrease in surface area from the tympanic membrane to the stapes is primarily responsible for the efficiency of sound transfer from the tympanic membrane to the cochlea. The lever-like arrangement of the ossicles provides additional mechanical advantage (Fig. 17-4C).

TWO MUSCLES MODULATE SOUND TRANSFER THROUGH THE MIDDLE EAR

As its name suggests, the tensor tympani muscle modulates the tension of the ear drum. The tensor tympani stretches from the malleus to the side of the Eustachian tube. When the muscle contracts, the malleus is pulled medially, and this in turn pulls on and therefore tightens the tympanic membrane (Fig. 17-4D). Just as is the case when a drum head is tightened, tightening the tympanic membrane increases the frequency and decreases the amplitude of vibrations. Recall from Chapter 10 that the trigeminal nerve innervates the tensor tympani along with the muscles of mastication. It is thought that the tensor tympani contracts in

OTOSCLEROSIS INVOLVES THE BONY ATTACHMENT OF THE STAPES TO THE TEMPORAL BONE SURROUNDING THE OVAL WINDOW.

In **otosclerosis**, the stapes forms a bony attachment to the temporal bone that circles the oval window. If stapes movement is restricted or blocked altogether, conductive hearing loss results, usually in both ears. For reasons that remain unclear, **tinnitus**, or ringing in the ear, accompanies hearing loss in many patients.

About half of the cases of otosclerosis are sporadic, meaning that they occur apparently by chance and certainly for reasons that we cannot identify. The other half of otosclerosis cases have a genetic basis, with most of those produced by an autosomally inherited dominant mutation. Although most familial cases of otosclerosis show a dominant pattern of inheritance, the penetrance of the disease is only about 40%, meaning that 60% of the individuals who inherit the mutation do not develop the disease. It appears likely that mutations in several different genes, including some inherited through a recessive pattern, can give rise to otosclerosis.

Patients with otosclerosis typically present with hearing loss in their twenties. Luckily, a straightforward

surgical treatment exists for this condition: replacement of the frozen stapes with a prosthetic device that acts like a piston on the inner ear. Often, post-surgical swelling transiently impairs conduction through the eighth cranial nerve, with the result that patients often experience transient hearing loss and/or vertigo, the latter reflective of vestibular damage. With time, these deficits usually resolve. An additional potential complication is **facial palsy**. The facial nerve courses through the middle ear, in the **internal acoustic meatus** that is normally separated from the middle ear chamber by a thin sheath of bone. However, in some people, the facial nerve is **dehiscent**, meaning that the nerve is not covered by a thin layer of bone but actually enters the middle ear chamber, sometimes coursing near or even across the oval window. In individuals with this condition, which is typically present bilaterally, facial palsy is a particular risk with any middle ear surgery. This consideration is important when surgical intervention on both ears is required or when a surgical redo is needed.

advance of both chewing and speech in order to decrease the loudness of sounds arising from those activities.

Contraction of the second middle ear muscle, the **stapedius**, pulls the stapes back away from the oval window (Fig. 17-4D). When the stapedius is contracted, the stapes cannot hit the oval window as hard, and this reduces the amount of pressure that is communicated to the cochlea. In response to loud noises—over about 70–80 dB—the stapedius contracts within about 100 ms, resulting in an attenuation of ensuing sounds by up to 40 dB.

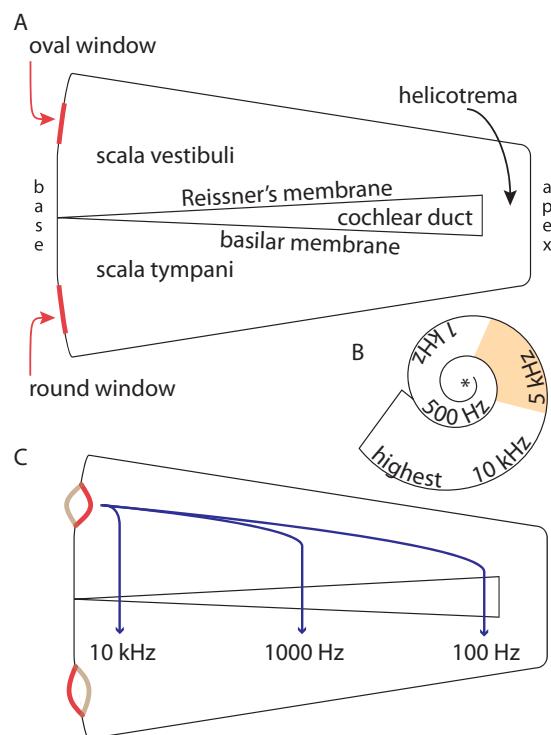
THE SENSORY REGION OF THE COCHLEA SITS WITHIN THE CENTER OF A U-SHAPED FLUID-FILLED TUBE

The three-dimensional anatomy of the inner ear is complicated, as the cochlea forms a spiral, wide at its base and narrow at the apex. Yet, if we unroll the spiral and look at the flattened cochlea, the essential organization is fairly

simple (Fig. 17-5). At the base of the fluid-filled cochlea is the oval window upon which the stapes presses. The stapes moves the oval window toward and away from a U-shaped, fluid-filled cochlear compartment composed of two different regions joined by a narrow canal. The region adjoining the oval window is the **scala vestibuli** or the **vestibular canal**. The scala vestibuli runs from the oval window at the base of the cochlea to the tip of the cochlear spiral where it connects, through the **helicotrema** to the **scala tympani** or the **tympanic canal**. At the basal end of the scala tympani is the **round window**, a membranous structure similar to the oval window. Because of the connection at the helicotrema, there is no actual divider between the fluid-filled scala vestibuli and scala tympani.

Between the scala vestibuli and scala tympani runs the **cochlear duct**, the **sensory region of the cochlea**. The cochlear duct spirals up the center of the bony cochlea but has the opposite orientation, with a narrow base and a wide apex (Fig. 17-5A). The cochlear duct separates the scala vestibuli and scala tympani for most of their lengths, ending just short of the cochlear apex, where the helicotrema joins the two canals. The cochlear duct shares one wall with the scala vestibuli and one wall with the scala tympani. The wall between the cochlear duct and the scala tympani is the **basilar membrane**, and the separation between the scala vestibuli and the cochlear duct is **Reissner's membrane**. Like the scala vestibuli and scala tympani, the cochlear duct is filled with fluid (see more below). Importantly, the **cochlear duct is flexible**, so that **pressure waves move the cochlear duct up and down**, meaning toward the scala vestibuli or toward the scala tympani.

Figure 17-5. A: The inner ear is illustrated in a simplified diagram of the unrolled cochlea. The scala vestibuli, cochlear duct, and scala tympani are all fluid-filled compartments within the **cochlea**. Reissner's membrane separates the cochlear duct from the scala vestibuli, and the basilar membrane separates the cochlear duct from the scala tympani. The helicotrema is a narrow channel that connects the scala vestibuli and scala tympani at the apex of the cochlea. Movement of the oval window sends a pressure wave through the scala vestibuli. The pressure wave crosses through the cochlear duct, and then moves down the scala tympani to impact the round window. B: A rough outline of the tonotopy in the cochlea is illustrated on a cartoon of the bony cochlea viewed from the apex (asterisk). The shaded region shows the area where most speech processing occurs. C: Compression at the oval window (red arcs). Conversely, rarefaction at the oval window results in compression at the round window (dim brown arcs). Pressure waves of different frequencies pass through the cochlear duct at different locations along the base-to-apex axis. The highest frequency sounds, about 20 kHz, displace the cochlear duct at the base, and the lowest frequency ones, about 5–10 Hz, at the apex. Note that the bony cochlea is wide at its base and narrow at the apex but that the orientation of the cochlear duct is reversed, narrow at the base and wide at the apex.



INPUT AT THE OVAL WINDOW IS TRANSFORMED INTO A WAVE OF MOVEMENT ACROSS THE COCHLEAR DUCT

When the stapes hits the oval window, a pressure wave travels up the scala vestibuli and then across the cochlear duct to the scala tympani before traveling down the scala tympani to the round window (Fig. 17-5C). As the cochlea is surrounded by unyielding bone, two pressure valves are needed to support any movement of the fluid within. Just as liquid does not come out of a single pinhole in a soda can, *movement of the oval window only produces a pressure wave because a second compressible portal, the round window, exists.* Compression at the oval window results in rarefaction at the round window, and rarefaction at the oval window produces compression of the round window.

Airborne sounds that arrive at different frequencies set up movements of the oval window at corresponding frequencies. The movement of the oval window in turn sets up a pressure wave at a given frequency that travels through the cochlea. Pressure waves of decreasing frequencies cross the cochlear duct at increasingly more apical points along the cochlear spiral (Fig. 17-5B–C). Thus, pressure waves at the highest frequency represented in the cochlea, 20,000 Hz, move the cochlear duct at the base of the spiral and pressure waves with low frequencies, of less than 200 Hz, move the cochlear duct closest to the helicotrema.

An important mechanism of tonotopy is the flexibility of the stiffest part of the cochlear duct, the basilar membrane. Recall that the basilar membrane forms the border between the cochlear duct and the scala tympani. At the base of the cochlear spiral, the basilar membrane is narrow and at the cochlear apex, the basilar membrane is wide (Fig. 17-5A). Note that the dimensions of the bony cochlea and those of the cochlear duct are inversely arranged:

- The narrowest part of the cochlear duct is located at the base of the bony cochlea, its widest part.
- The wide apex of the cochlear duct is located at the narrow apex of the bony cochlea.

The narrow basilar membrane at the base of the cochlea is most taut and therefore moves maximally in response to a high-frequency pressure wave. In contrast, at the apex of the cochlea, the wide basilar membrane is relatively loose and bends maximally in response to low-frequency pressure waves. Consequently, the cochlear duct including the basilar membrane moves maximally in response to sounds of sequential frequencies. This topographic arrangement of maximal pressure wave excursion along the length of the cochlea follows a **tonotopic** organization. The tonotopy of the basilar membrane dictates a tonotopic neural response to sound, so that the apical cochlea responds best to low-frequency sounds and the basal cochlea responds best to sounds of increasing frequency (see Box 17-9). The frequency that produces the greatest movement of the basilar membrane, and consequently the greatest hair cell response at any one point within the cochlea, is termed the **characteristic frequency**.

COCHLEAR IMPLANTS TAKE ADVANTAGE OF TONOTOPY TO PROVIDE HEARING TO DEAF INDIVIDUALS.

Cochlear implants have allowed children born deaf and adults who have recently lost their hearing to participate in and communicate with the hearing world. Cochlear implants are optimal for individuals with loss of hearing due to hair cell failure. A working auditory nerve and intact central auditory pathways are necessary for a cochlear implant to succeed. Cochlear implants even allow patients to talk on a telephone, meaning that cochlear implants restore hearing to a level where acoustic information alone supports language comprehension.

Cochlear implants receive and process sound, emphasizing frequencies present in human speech. The different frequency components are separated out using Fourier analysis and different parts of the cochlea are accordingly stimulated so that, for example, when high-frequency sounds occur, the cochlea is stimulated close to the base. Most cochlear implants operate by producing a constant rate of electrical pulses that is amplitude-modulated to reflect the frequencies contained in incident sound. Remarkably, some individuals achieve fairly reliable speech recognition with only one channel of stimulation! In truth, the reasons for the remarkable efficacy arising from implants with a single channel remain unclear. Although some cochlear implants

employ more than 20 channels of stimulation, each consisting of an electrode located at a specific site in the cochlea, it appears that five to eight channels is sufficient to allow for speech perception in most patients.

Implanting a cochlear device does not miraculously make a deaf person hear. After the operation, the patient must relearn, or learn in the case of a prelingual infant, to hear, to decipher the meaning of the electrical pulses emitted by the cochlear implant. This learning process is neither a simple nor a quick task, as described by Michael Chorost in his book *Rebuilt: My Journey Back to the Hearing World*. Chorost was born hard of hearing and only learned to talk at age 3, after receiving hearing aids. He lost all residual hearing on a summer day in his mid-thirties. Months later, a cochlear device was implanted into Chorost's cochlea. Chorost worked hard for months learning to interpret the input from his cochlear implant, concluding that the successful use of an implant required the user to become an expert "athlete of perception," to practice hearing, devise tricks, and learn rules. As with vision, hearing is learned, and learning the new language of a cochlear implant as an adult is a challenging process.

SENSORY TRANSDUCTION OCCURS IN A SUBDIVISION OF THE COCHLEAR DUCT CALLED THE ORGAN OF CORTI

A small region, pie-shaped in cross section, located on the basilar membrane side of the cochlear duct comprises the **organ of Corti**, the site of sensory transduction within the cochlear duct (Fig. 17-6). Dividing the organ of Corti from the rest of the cochlear duct is the **tectorial membrane**, which emanates outward from the **modiolus**, the central pillar of the cochlear spiral. Sensory hair cells sit atop the basilar membrane and extend cellular extensions termed stereocilia toward the tectorial membrane (much more on this below). Movement of the stereocilia constitutes the adequate stimulus for hair cell transduction.

Cochlear hair cells come in two varieties: **inner** and **outer hair cells**. The human cochlea contains about 3,500 inner hair cells arranged in a single row close to the

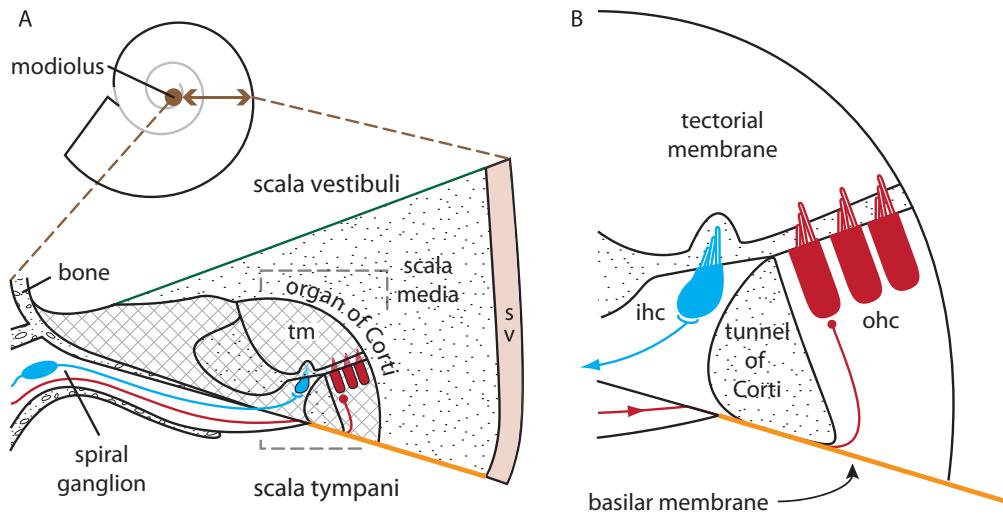


Figure 17-6. A: The organ of Corti occupies the inner portion of the cochlear duct extending outward from the modiolus, the central pole around which the cochlea turns. At the outer edge of the cochlear duct is a specialized tissue, the stria vascularis (sv), which pumps potassium ions in to form endolymph. Endolymph is a potassium ion-rich fluid that fills the scala media, the fluid-filled portion of the cochlear duct. The organ of Corti contains two types of hair cells, inner and outer, supporting cells, and the tectorial membrane (tm). Spiral ganglion cells (blue) innervate a single row of inner hair cells (blue) and carry afferent input from the inner ear to the cochlear nuclei. Efferents arising from cells in the pons (maroon) innervate three rows of outer hair cells (maroon). Outer hair cell function serves as the cochlear amplifier. B: The stereocilia of outer hair cells (ohc) are embedded in the tectorial membrane. When a sound elicits a pressure wave in the cochlea, the basilar membrane moves up and down at the frequency of the incident sound. If the frequency of basilar membrane movement matches the characteristic frequency of the hair cells at the cochlear location, the outer hair cells themselves will move up and down (Fig. 17-7). The movement of outer hair cells serves as an independent resonator (Fig. 17-8), which amplifies the movement of the basilar membrane. The stereocilia of inner hair cells (ihc) float within the endolymph and respond to pressure waves produced by basilar membrane movement and the movement of endolymph. The responses of inner hair cells are conveyed to spiral ganglion cells through a synapse. The outer hair cells receive input from the central nervous system. As the stereocilia of the outer hair cells are embedded within the tectorial membrane, particularly large displacements of the tectorial membrane could lead to a shearing of the stereocilia. Very loud sounds may produce sufficient movement of the tectorial membrane and shearing may be the mechanism underlying acute acoustic trauma. Unfortunately, hair cells do not regenerate stereocilia. Therefore, injuries to the stereocilia of hair cells produce permanent damage.

modiolus and about 12,000 outer hair cells arranged in three rows farther from the modiolus. Although both inner and outer hair cells are sensitive to basilar membrane displacement, the functional significance of inner and outer hair cell activation differs in fundamental ways. The *inner hair cells are the source of auditory information bound for perceptual pathways* and comprise the input to more than 90% of the auditory afferents in the eighth cranial nerve. Outer hair cells do not contribute input to central auditory pathways but are critical to normal hearing as they fine-tune the tonotopy of basilar membrane movements and consequently of inner hair cell responses. Essentially the outer hair cells serve as the cochlear amplifier.

THE FLUID WITHIN THE ORGAN OF CORTI IS AT A POSITIVE POTENTIAL WITH RESPECT TO GROUND

Most of the vestibular labyrinth contains **perilymph**, which is similar to extracellular fluid elsewhere in the body. In contrast, **endolymph**, the fluid in the cochlear duct and in the sensory regions of the semicircular

canals and otoliths, is rich in potassium as well as sodium ions. Endolymph has a positive potential with respect to perilymph and interstitial fluid. In fact, the **endocochlear potential** is roughly +80 mV. The potassium ions that are key to endolymph composition are pumped out by cells in the **stria vascularis**, a highly vascularized tissue that lines the outside of the cochlear duct (Fig. 17-6A). The endolymph fills the **scala media**, the fluid-filled space in the cochlear duct.

OUTER HAIR CELLS FINE-TUNE THE FREQUENCY RESOLUTION OF THE COCHLEA

The paucity of input from outer hair cells to auditory pathways suggests that outer hair cells do not make a major contribution to auditory perception. Yet, outer hair cells are sensitive to basilar membrane displacement. Further, hearing loss typically results from the loss of *outer* rather than inner hair cells. What contribution do outer hair cells make that is so critical to hearing? The answer is one of the most intriguing stories of basic neurobiology to emerge over the last half century. Outer hair cells are so important to hearing because they boost the *stimulus* that reaches the inner hair cells. When activated, outer hair cells *move*—they actually shorten and lengthen their cell body (Fig. 17-7). The movement of the outer hair cells amplifies the excursion of the basilar membrane and fluid movement within the organ of Corti (Fig. 17-8). *The ultimate result of outer hair cell function is that the stimulus to the inner hair cells is amplified.* Amplification is greatest for pressure waves at the characteristic frequency. Thus, outer hair cells serve as independent resonators that amplify the movement of the basilar membrane (Fig. 17-8). Because outer hair cells amplify the stimulus to which the inner hair cells respond, outer hair cells are often termed the *cochlear amplifier*.

It is important to put the contributions of outer hair cells to cochlear tonotopy into context. As detailed above, the flexibility of the basilar membrane produces a

Figure 17-7. Outer hair cells contain a transmembrane protein, called *prestin*, that serves as their molecular motor. When the stereocilia of the outer hair cell bend in the preferred direction, toward the tallest stereocilia, the cell depolarizes. Depolarization causes prestin to change its conformation, with the result that outer hair cells shorten in length. Thus, when the outer hair cell depolarizes, the outer hair cell shortens in length, and when it hyperpolarizes, the outer hair cell lengthens. Changes in outer hair cell length move the basilar membrane up and down and thereby amplify fluid pressure waves in the cochlear duct. Ultimately, movement of the hair cell greatly increases the displacement of the basilar membrane over what it would be from passive mechanisms alone.

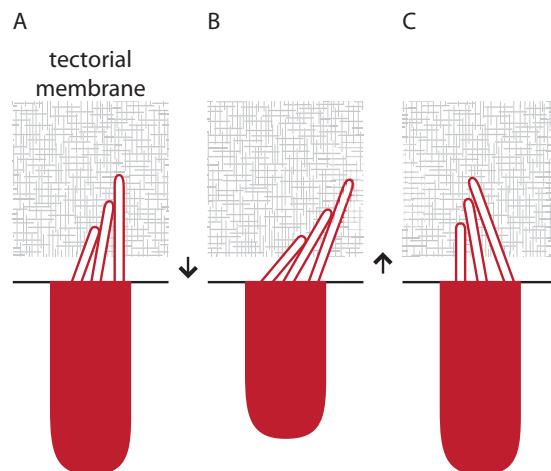
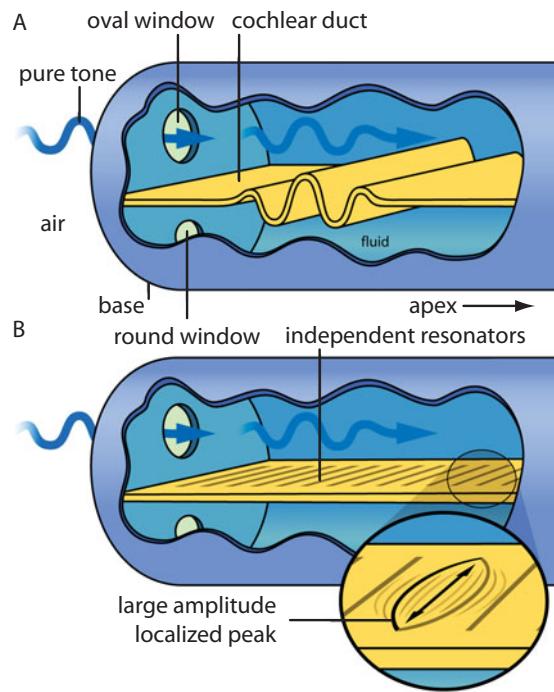


Figure 17-8. A: The effect of a travelling pressure wave on the basilar membrane is shown in a cartoon of the uncoiled cochlea. The location of the peak displacement of the membrane depends roughly upon the frequency of the wave. However the resolution of the tonotopy through this passive amplification is not sufficient to explain perceptual discrimination offrequencies that differ by only a few Hz. B: The additional resolution is provided by the outer hair cells, which serve as independent resonators at their characteristic frequency.

Modified from Bell, A. Hearing: Travelling wave or resonance. *PLoS Biol* 2:e337, 2004, with permission.



pressure wave that has maximal displacement at progressively lower frequencies as one moves from the base to the apex of the cochlea. Although the tonotopy due to the pressure wave alone is crude, humans can resolve very small differences in frequency. For example, a pressure wave with a frequency of 500 Hz moves the basilar membrane across a wide stretch corresponding to characteristic frequencies of 450–550 Hz. Yet, we can distinguish between tones at very close frequencies, for example between tones with frequencies of 500 Hz and 501 Hz. The outer hair cells increase the resonance of the basilar membrane and thereby provide the added resolution to cochlear tonotopy (see Box 17-10). Without the outer hair cells, inner hair cells have flat tuning curves (Fig. 15-3), and only respond to stimulation at the characteristic frequency when it is quite loud. For example, a hair cell that normally responds to its characteristic frequency presented at a few dB will only respond to that same frequency presented at more than 80 dB, in the absence of outer hair cells. Unfortunately, outer hair cells are sensitive to a number of environmental conditions, including loud noises accumulated over a lifetime (see Box 17-11), as well as certain antibiotics and chemotherapeutics (see Box 17-12).

OUTER HAIR CELLS PRIMARILY RECEIVE INPUT FROM THE CENTRAL NERVOUS SYSTEM

As everyone knows, sensory information from the outside or internal world is transmitted to pathways in the CNS that result in perception and other reactions. Yet, very few afferent fibers from the spiral ganglion contact outer hair cells. Instead, there is a dense innervation of the outer hair cells by pontine

MATCHING THE BASILAR MEMBRANE'S NATURAL RESONANT FREQUENCY GREATLY AMPLIFIES BASILAR MEMBRANE MOVEMENT.

Outer hair cells use resonance matching to effectively amplify basilar membrane oscillations. The mechanism of natural resonance amplification is a potentially powerful one that has caused bridges to collapse, glass to shatter, and cars to vibrate. To understand this, we first need to understand that everything has a natural resonance frequency or frequencies. Drinking glasses resonate at higher frequencies than do car doors. Regardless of the particular frequency, adding energy in the form of pressure waves or sound at an object's resonant frequency has the effect of greatly increasing the object's oscillatory movements at that frequency. Thus, a very loud bass sound from a car radio shakes the car body. In the same way, belting out a tone at the resonant frequency of a wine glass will first lead to the glass's vibrating, and ultimately to its shattering. Unfortunately, this same principle has led to the demise of at least two bridges, one from wind and one or more from the rhythmic marching of soldiers at the bridges' natural resonant frequencies. A number of structural fixes—wider, heavier spans and mechanical dampeners—are

commonly used today to avoid bridge collapse due to winds at the bridge's resonance frequency. To prevent bridges from collapsing under soldiers, soldiers have broken cadence when crossing bridges for the last century and a half.

The resonant frequency of the basilar membrane varies progressively from the basal turns of the cochlea to the apex. This is an intrinsic property of the basilar membrane. Basally, the basilar membrane has the highest resonant frequencies, and apically the resonant frequency of the basilar membrane is lowest. The movement produced by stimulated outer hair cells produces the greatest amplification of basilar movement at the location with the matching resonant frequency. Thus, even if outer hair cells across a wide area are stimulated by a pressure wave, the effect of the movement produced by the outer hair cells is greatest at one particular location. In this way, the gross tonotopy of the pressure wave combines with the independent resonance created by the outer hair cells to generate a very fine tonotopy in the cochlea.

neurons! The fact that outer hair cells receive input from the CNS fits with the motor function of these cells (see Box 17-13). Moreover neurons in the pons that contact outer hair cells use acetylcholine, the transmitter common to all motor output neurons (see Chapter 7). Thus, we can think of the outer hair cell as a very small “muscle.” When acetylcholine is applied onto an outer hair cell, movements are suppressed. Thus, input from pontine neurons may serve to dampen the sensitivity of outer hair cells in anticipation of expected sounds. Remarkably, the connection from pontine neurons to outer hair cells allows the CNS to influence the most peripheral aspect of hearing, the stimulus itself.

STIMULATION ELICITS ENTRY OF POTASSIUM IONS INTO HAIR CELL STEREOCILIA

Hair cells of all types and locations are mechanosensitive and respond to movements of the stereocilia that adorn their apical surface. The so-called stereocilia are not, in fact, cilia at all but long extensions from the cell body

NOISE DAMAGES THE ORGAN OF CORTI AND CAUSES IRREVERSIBLE HEARING LOSS.

A revealing study more than a half century ago showed that Mabaan tribespeople in the Sudan, who had not been exposed to modern noises, suffered from minimal hearing loss as they aged. Seventy-year-old Mabaans had the hearing of 20-something Americans. Although many differences between the Sudanese tribespeople and the Americans could account for the difference in age-related hearing, we know that at least one factor is noise exposure. Very loud noises, 125–130 dB at many frequencies, kill hair cells acutely. Moreover, chronic exposure to noises common to modern life can lead to irreversible damage to the organ of Corti. Even listening to portable devices using ear buds may eventually lead to hearing loss.

Loud noises damage hearing by effects on three primary targets:

- **Outer hair cells:** The stereocilia of outer hair cells are embedded in the tectorial membrane. Normally, the displacement of the basilar membrane with respect to the tectorial membrane stimulates outer hair cells. Loud noises may actually lead to stereocilia being sheared off of the outer hair cells. This is an irreversible loss as new hair cells are not made. The stereocilia of inner hair cells are not embedded in the tectorial membrane and therefore are not vulnerable to the same type of shearing damage as outer hair cells.
- **Membranes of the organ of Corti:** The membranes that keep the cochlear duct intact and separate the duct from the perilymph-filled compartments can be ruptured by loud noises.

- **The stria vascularis:** A compromise of the endocochlear potential, normally at +80 mV, leads to diminished hair cell function. Without the strong driving force between endolymph and the hair cell, all sounds will be less effective in depolarizing hair cells and therefore in exciting spiral ganglion cell afferents.

Genetic factors render some people particularly vulnerable to noise-induced hearing loss. For example, mutations in a potassium channel found in the stria vascularis have been associated with severe noise-induced hearing loss in people. There is overlap in the mechanisms of noise-induced hearing loss and **presbycusis** (ancient Greek for *old man-hearing*), or age-related hearing loss. Certainly, the modern world is a noisy place, and virtually all of us experience at least some hearing loss as we age. Yet, some mechanisms may contribute to presbycusis and not noise-induced hearing loss and vice versa.

Most individuals with presbycusis typically show a loss of high-frequency hearing, and in most cases this is due to a loss of outer hair cells. Hearing loss makes speech sound muffled and quiet. In a noisy environment, understanding speech becomes extremely difficult for individuals with hearing loss. Although hearing aids amplify sounds across all frequencies, or in some cases across the frequencies of human speech, they cannot provide the very local amplification provided by the outer hair cells. Nor can hearing aids restore sensitivity to high frequencies. Consequently, hearing aids do not restore perfect hearing.

that contain an inner actin skeleton. The stereocilia are arranged from short to tall, with thin proteinaceous tip-links linking shorter stereocilia to their taller neighbor. When the stereocilia are bent toward the tallest stereocilium, the tip-links pull on the **mechanoelectrical transduction** or **MET channel** to increase the probability of channel opening. When the stereocilia are bent away from the tallest stereocilium, the probability that the mechanoelectrical transduction channel will close increases. At rest, a portion of transduction channels are open and the hair cell's resting membrane potential is about -50 mV (Fig. 17-9).

When the stereocilia of a hair cell are bent toward the tallest stereocilia, the *preferred direction*, and mechanoelectrical transduction channels open, potassium ions

Box 17-12

AMINOGLYCOSIDE ANTIBIOTICS AND CHEMOTHERAPEUTICS EXERT TOXIC EFFECTS ON HAIR CELLS.

The aminoglycoside antibiotics, the chemotherapeutic agent cisplatin, diuretics, and even high doses of salicylates such as aspirin kill hair cells in a minority of patients. Ototoxic antibiotics have a predilection to kill either cochlear or vestibular hair cells, with neomycin, kanamycin, and amikacin acting primarily in the cochlea. The mechanisms of toxicity are diverse. Through mechanisms that remain somewhat controversial if not mysterious, ototoxic drugs are internalized into hair cells. Within hair cells, ototoxic drugs set off apoptosis, or a program of cell death. The cochlear hair cells most at risk for ototoxicity are the *outer hair cells in the basal turns of the cochlea*. Loss of basal outer hair cells leads to a loss

of hearing in the high-frequency range and, for unknown reasons, also often causes **tinnitus**.

Although the proportion of patients suffering ototoxic hearing loss is relatively small, the consequences for affected patients are devastating. Furthermore, the prescription of some ototoxic compounds can be avoided as often alternative therapeutics exist. When prescription of a potentially ototoxic compound is warranted, close monitoring of serum levels should be used to prevent audiologic or vestibular damage. Since genetic factors may predispose some to ototoxic damage, patients with a family history should be particularly carefully managed.

Box 17-13

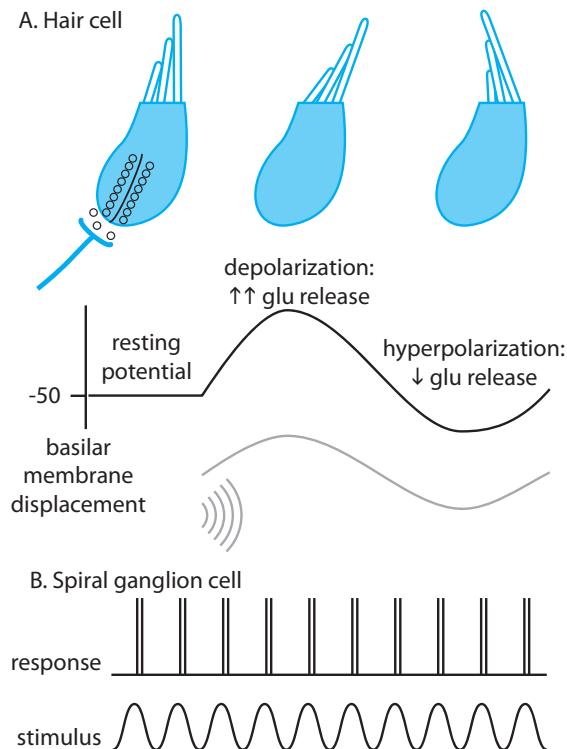
OTOACOUSTIC EMISSIONS RESULT FROM OUTER HAIR CELL ACTIVATION.

Consider how sound reaches outer hair cells. Now imagine that that pathway is reversed, so that activation of an outer hair cell *initiates* a sequence of events that ends with a sound *coming out* of the ear. Let us go through this step by step. When the outer hair cell is activated, it moves and sets up a local resonance at the characteristic frequency. This movement produces movement of the basilar membrane, which travels to the oval window and moves the middle ear muscles, in reverse. First, the stapes moves, and this moves the incus, which in turn moves the malleus. The malleus is attached to the crown of the tympanic membrane and so movement

of the malleus moves the tympanic membrane. Movement of the tympanic membrane produces sound in a manner analogous to the production of sound from a woofer.

Otoacoustic emissions can occur spontaneously but can also be elicited by a sound. For instance, a tone will elicit an emission of the same frequency. Since otoacoustic emissions depend on healthy outer hair cells, the presence of evoked otoacoustic emissions can be used as an early test for cochlear health. This test is particularly useful for testing the hearing of babies, young children, and other nonverbal individuals.

Figure 17-9. Hair cells, like other non-neuronal sensory cells, use graded potentials and do not fire action potentials. The resting potential of hair cells is about -50 mV. When a sound occurs and a pressure wave moves the basilar membrane (gray), the stereocilia of the hair cell are bent. When the stereocilia bend toward the tallest stereocilium, the preferred direction, the hair cell depolarizes, and when the stereocilia bend away from the tallest stereocilium, the hair cell hyperpolarizes. When the membrane potential is depolarized above the resting potential, release of neurotransmitter is increased. The release of more glutamate (glu) vesicles increases the probability of an action potential in the postsynaptic spiral ganglion cell. **B:** In response to a pressure wave of 3 kHz or less (stimulus), a spiral ganglion cell fires one or more action potentials in response to each cycle. The number of action potentials fired per cycle is greater as the amplitude of the stimulus increases. Note that the response is phase-locked, meaning that it occurs at the same phase of the stimulus during each cycle.



depolarizes. The most important consequence of outer hair cell depolarization is a shortening of the outer hair cell (Fig. 17-7), whereas the critical consequence of inner hair cell depolarization is an increase in neurotransmitter release (Fig. 17-9A). Particularly fast potassium channels, present in the membrane of the hair cell soma, are activated by depolarization and are responsible for repolarizing hair cells quickly. Rapid repolarization of hair cells allows the hair cell membrane potential to follow sounds with frequencies of up to $3,000$ Hz or so (Fig. 17-9A). For example, vibration of the basilar membrane at $1,000$ Hz alternately moves the basilar membrane sinusoidally up and down every millisecond. Because of the fast repolarization mechanisms in hair cells, hair cells show a sinusoidal response of alternating depolarization and hyperpolarization with a period as short as 1 ms. However hair cells cannot follow the sinusoidal movements at frequencies greater than $3,000$ Hz or so. Sounds above frequencies of $3,000$ Hz produce a sustained depolarization of hair cells at the corresponding tonotopic location.

STIMULUS FREQUENCY IS CODED BY BOTH LABELED-LINE MECHANISMS AND DISCHARGE PATTERN

Each inner hair cell is innervated by, on average, eight afferents from the spiral ganglion. The spiral ganglion cells have somata that sit just inside the organ of Corti within the bony cochlea (Fig. 17-6A). When a pressure wave arrives, hair

cells respond by releasing neurotransmitter in a pattern that reflects the incident sound. Consider a 500 Hz tone. Close to the apex of the cochlea, the basilar membrane will resonate at 500 Hz, and the inner hair cells there will respond with alternating depolarizations and hyperpolarizations every 2 ms (= the period of a 500 Hz stimulus). Neurotransmitter release mirrors the hair cell's membrane potential. As a result, the postsynaptic auditory afferents in the eighth cranial nerve tend to fire every 2 ms (Fig. 17-9B). The location of the hair cell and the identity of the auditory afferent brand the stimulus as having a characteristic frequency of 500 Hz. In addition, the afferent fires action potentials that occur with a frequency of 500 Hz. Neither hair cells nor auditory afferents can follow sounds at the characteristic frequencies of the basal turn of the cochlea, frequencies greater than 3,000 Hz. Therefore, auditory afferents coding for sounds at frequencies above 3,000 Hz employ the labeled-line mechanism for coding.

CENTRAL AUDITORY STRUCTURES CARRY INFORMATION FROM BOTH EARS

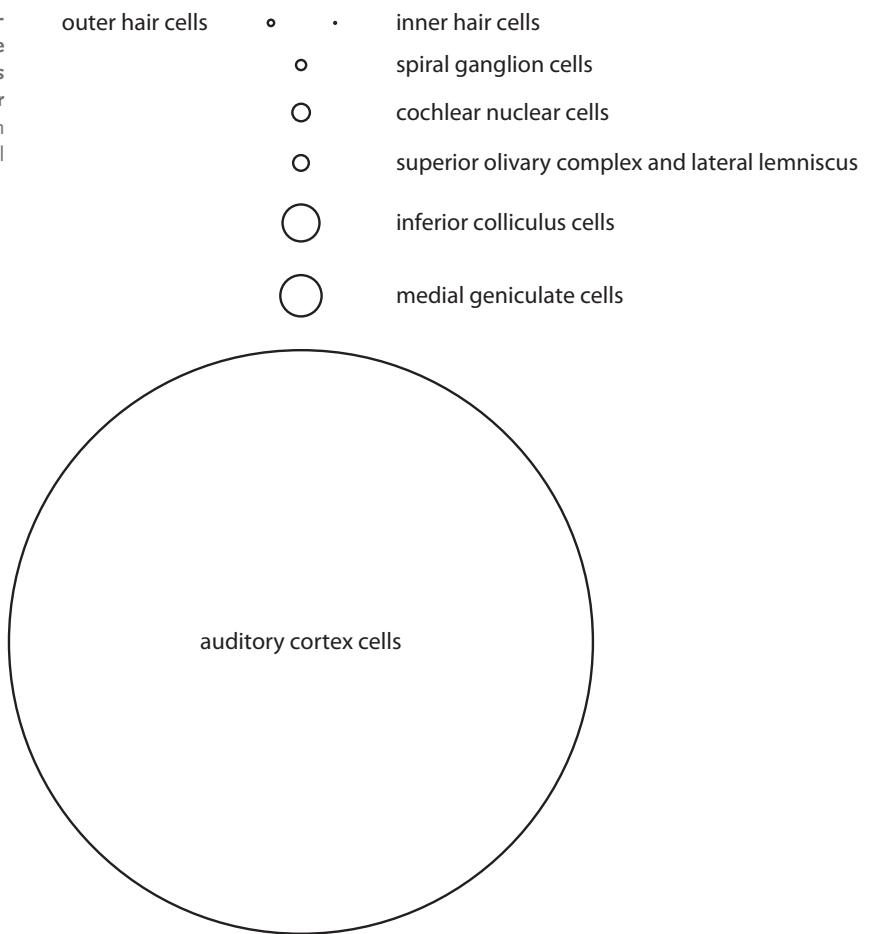
As illustrated in Figure 12-7, the cochlear nucleus projects bilaterally to target nuclei. There are even some commissural connections between the cochlear nuclei. The result of these connections is that third-order and in some cases even secondary sensory neurons in the auditory pathway carry information about sound arriving at both ears. Neurons in the inferior colliculus and in the medial geniculate nucleus carry bilateral auditory information. Thus, despite the fact that central neurons involved in hearing pathways greatly outnumber hair cells (Fig. 17-10), hearing cannot be impaired by a singular central lesion. Rather deafness is always caused by a peripheral lesion (see Box 17-14).

SPEECH PRODUCTION USES A FUNDAMENTAL FREQUENCY SET BY VIBRATIONS OF THE GLOTTIS

The most important function of audition is to facilitate communication through spoken language. Before jumping from the auditory nerve to the cortex to discuss the mechanisms of speech *comprehension*, we take a brief detour to understand speech *production*.

The first step in speech production is **phonation**, which means pushing an air stream through the **glottis**, between the **vocal folds** of the larynx (Fig. 17-11). The glottis is pushed open when the lungs push air at a sufficient pressure. After being pushed open, the vocal folds collapse to a closed position, and then the glottis is pushed open again by the air pressure exerted by the lungs, and so on. In this way, the glottis opens and closes many times in a second to produce the **fundamental frequency** of speech. The tension in the vocal folds and the distance between them determine the

Figure 17-10. The area of each circle is proportional to the number of cells contained in the labeled region. The number of inner hair cells is less than a third of the number of outer hair cells. The total number of hair cells is in turn dwarfed by the number of cells in central auditory pathways.



fundamental frequency, which for men is about 120 Hz and for women is about 250 Hz. The fundamental frequency of speech carries social meaning without semantic content (see Box 17-15).

The fundamental frequency of speech changes from the beginning to the end of a sentence. The change of frequency across the course of a sentence is different for a statement and for a question. Different emotions induce people to speak with different fundamental frequencies. All of these forms of modulation of the fundamental frequency are part of **prosody** (see Box 17-16). The same words, when spoken with two different intonations and rhythms, can have two entirely different meanings. “Have a nice day,” spoken at normal pace and frequency communicates that the speaker indeed hopes that you will have a pleasant day. Yet, when slowed down and spoken at a lower frequency, the meaning of the sentence is exactly the opposite: when intoned sarcastically, “Have a nice day,” actually means that the last thing that the speaker wants is for you to have a pleasant day and would in fact prefer that you have a rotten, stressful day. Facial expressions, such as a roll of the eyes, aid in the communication of the intended sarcasm. Strokes in the right hemisphere, as well as some diseases, are accompanied by deficits in either understanding or producing prosodic speech (see Box 17-17).

COCHLEAR FUNCTION DEPENDS ON A REMARKABLY LARGE NUMBER OF GENE PRODUCTS.

In contrast to people with hearing loss, deaf people cannot hear at all. Deafness is caused by a total loss of hair cell function. Hearing aids are not helpful, but cochlear implants can provide acoustic information to the brain if the spiral ganglion afferents are intact as is typically the case. In children, most deafness is caused by genetic defects whereas in adults, deafness is typically the result of ototoxic drugs and/or exposure to noise. The genetic analysis of congenital deafness in humans has provided important clues to understanding the molecular mechanisms of hearing. In the reverse direction, molecular investigations into the basic mechanisms of hearing have led to the discovery of novel genetic causes of deafness. The rich interplay between human deafness and molecular mechanisms of hearing is rooted in the large number of molecules involved in cochlear function. *About 1% of the coded genes in the human genome contribute to peripheral hearing function, and many of the molecules serve no other known function.* As a result, most congenital deafness disorders are nonsyndromic, meaning that hearing is the only affected system. Genetic mutations cause nonsyndromic congenital deafness through effects on multiple targets:

- **The tectorial membrane:** Proteins including collagens and **tectorins** are integral components of the tectorial membrane. A set of anchoring proteins are involved in securing the tectorial membrane within the organ of Corti.
- **Hair-cell stereocilia:** The actin core of the stereocilia is stabilized and extended by interactions with several proteins, including a number of myosin isoforms and a protein “glue” called **harmonin**.
- **Outer hair-cell motility:** The motor protein in the outer hair cells is **prestin**. Mutations in prestin cause **deafness**, providing compelling evidence of the importance of outer hair cell-mediated movements to hearing.
- **Synaptic transmission from the inner hair cell to spiral ganglion afferents:** Otoferlin serves as

the calcium ion sensor that triggers neurotransmitter release from hair cells, a role analogous to that played by synaptotagmin in neurons. In people with otoferlin mutations, sound is transduced normally but no sound-related activity occurs in the auditory nerve fibers.

- **Ionic homeostasis within the cochlear duct:** Defects in *connexins*, the gap junction building blocks introduced in Chapter 4, a potassium channel found in the stria vascularis, transporters, and several transmembrane proteins with as of yet undiscovered function, are all associated with deafness. Connexins are critical to both the formation of endolymph and the clearance of potassium ions from the interstitial fluid surrounding hair cell somata. Mutations in genes coding for connexins that are specifically found in the inner ear are the most common genetic cause of deafness.

In addition, to the nonsyndromic deafness disorders, deafness can be part of a syndrome, meaning that a group of symptoms run together. The most common syndrome of deafness along with vestibular impairment and blindness is **Usher syndrome**. Patients with Usher syndrome have a defect in any of about ten genes. The syndrome has varying severity afflicting some patients with deafness and others only with a hearing loss. In the most severe cases, patients are born deaf, quickly develop balance problems, and start losing vision by the age of 10 years.

A continued dialog between scientists and physicians is critical to the effective application of appropriate therapies to particular forms of congenital deafness. For example, if and when hair cell regeneration becomes a realistic therapeutic option, it will have to be used on individuals with hospitable cochlea. In other words, hair cell regeneration would be an inadvisable therapy for people whose deafness stems from a defective stria vascularis and consequently an inhospitable ionic environment in the cochlea.

THE FUNDAMENTAL FREQUENCY OF SPEECH COMMUNICATES SOCIAL STATUS.

The fundamental frequency of phonation in isolation sounds like a hum without any articulated words. Although the fundamental frequency contains no semantic content, it carries a high degree of communicative value. Over the course of a dialogue, the fundamental frequency of one speaker often changes to approach the other speaker's fundamental frequency. This convergence may serve a prosocial role in bringing the two speakers closer together. Reliably, the speaker who accommodates is perceived to be of a lower social status. In other

words, the more dominant individual in a conversation accommodates his or her fundamental frequency relatively little. For example, Larry King adapted his fundamental frequency to that of Bill Clinton, Barbra Streisand, Elizabeth Taylor, and Tip O'Neill but not to that of Dan Quayle, Jimmy Carter, or Spike Lee. Remarkably, from 1960 to 2000, the American presidential nominee who changed his fundamental frequency *less* was always the nominee who won the popular vote, although not the winner of the office in 2000.

THE VOCAL TRACT FILTERS THE SOUND WAVE EMANATING FROM THE GLOTTIS

The fundamental frequency of speech is the frequency recorded at the glottis. This frequency is the raw material for what we actually hear. The air pushed through the glottis is filtered by the **vocal tract** (Fig. 17-11), which consists of

PROSODY EXERTS A GREAT INFLUENCE ON THE MEANING OF OUR SPOKEN WORDS.

Prosody is the mechanism by which emotions are conveyed without verbal or semantic content. Posture and facial expressions are components of prosody. A smirk communicates a different emotional message than a frown. Acoustic features of our speech also comprise a large component of prosody. Acoustic features of prosody in nontonal languages such as English and other Indo-European languages include:

- **Frequency:** The same words spoken at a high frequency convey a different meaning than when spoken at a low frequency.
- **Loudness:** A whisper and a shout impart very different meanings.
- **Timing:** Speaking in a rapid slur and in a slow deliberate fashion lends different meanings to the same sentence.

Consider the everyday greeting of "Good morning." Spoken rapidly and softly in a low, steady voice, "Good morning" is a greeting by rote, a virtual automatism that has little personalized meaning. Such a greeting happens many times every day and rarely gives us pause. In contrast, a slowly articulated "Good morning" in a loud and melodic voice is nearly as eloquent as saying, "Wasn't last night fun? I am so happy to see you this morning."

Prosody exists in diverse languages, albeit in different forms. In tonal languages, such as Mandarin Chinese, many sub-Saharan languages, and Navajo, one syllable can have several different semantic meanings depending on intonation. Individuals who speak tonal languages use pitch to convey semantic meaning while employing timing and loudness to impart prosody.

DEFICITS IN PROSODY NEGATIVELY IMPACT SOCIAL INTERACTIONS.

Difficulty in either conveying or understanding the prosody of speech is termed **aprosodia**. Some diseases are accompanied by aprosodia. For example, individuals afflicted with depression or schizophrenia often speak with minimal modulation of fundamental frequency. Patients can also become aprodosic after either traumatic brain injury or a stroke affecting the nondominant hemisphere. These patients typically present with a complaint of difficulty in social interactions.

The neural substrates for aprosodia largely mirror the substrates for aphasia. Mirroring Wernicke's aphasia, aprosodia caused by a lesion in the temporoparietal region of the nondominant hemisphere affects the understanding or *comprehension* of prosody. In contrast, lesions in the frontal cortex of the nondominant hemisphere result in a problem with the *production* of prosodic language. Thus, both verbal articulation and the infusion of language with emotion depend on the frontal cortex just anterior of the face area of the motor strip, but the former is lateralized to the dominant hemisphere and the latter to the nondominant hemisphere. Similarly, the comprehension of language, including the emotional content of communication, depends on the superior temporal and inferior parietal cortex, with semantic understanding lateralized to the dominant hemisphere and prosodic understanding lateralized to the nondominant hemisphere.

Verbal articulation and intonation of prosody must be coordinated. In order to emphasize a word, we slow our articulation of *that word* and not the

word before or after. For example, consider the line, "The mouse ran up the clock" from the nursery rhyme, "Hickory Dickory Dock." By changing the word that is emphasized we call attention to the fact that:

A mouse rather than many mice or one specific mouse ran up the clock.

A *mouse* rather than a cat ran up the clock.

A mouse *ran* rather than ambled up the clock.

A mouse *ran up* rather than down the clock.

A mouse *ran up the* very singular clock rather than any old clock.

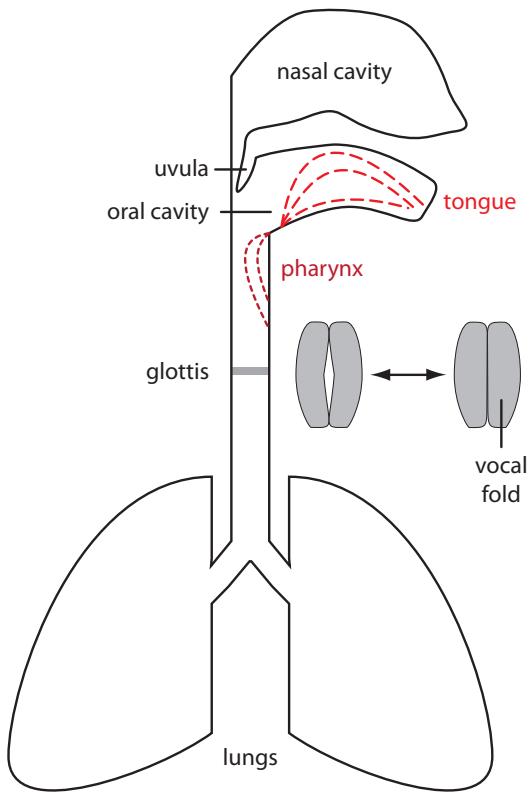
A mouse *ran up the clock* rather than the chair.

To emphasize a particular word, the articulation process, centered in the dominant hemisphere, must be coordinated with prosodic production in the nondominant hemisphere. Because of the required coordination between the two hemispheres, strokes in the dominant hemisphere can sometimes appear to impair prosody. One can test whether prosody per se is indeed affected by asking an individual to repeat a prosodic intonation using simple sounds rather than words. For example, a person who may not be able to intone "What a cute baby" may be able to copy the tone and prosody used while saying "ba ba ba ba ba." Thus, reducing the articulation demands may reveal either normal or impaired prosody.

the space between the larynx and the lips and the nostrils. The vocal tract is fundamentally a tube, and the length and shape of that tube influences the frequency of the vocalizations. Just as the very long contrabassoon has a very low range and the very short piccolo has a very high range, our vocalization frequency depends *in part* on the length of our vocal tract. The short vocal tract length of babies and children, along with laryngeal factors contributes to the high-pitched sounds that young people produce.

The shape of the vocal tract is even more important than simply the length of the vocal tract in the articulation of sounds. When filtered by different configurations of the vocal tract, the same phonation produces different sounds. For example, we lift our tongue caudally and purse our lips to articulate the "oo" sound in "who," while we

Figure 17-11. A schematic of the human vocal tract is illustrated. Air from the lungs is placed under pressure from contraction of the diaphragm (not shown). When a sufficient pressure is reached, the vocal folds are pushed apart and the glottis opens (left inset). The pressure quickly dissipates and the glottis closes (right inset). The glottis opens and closes at a frequency that is the fundamental frequency of speech, 100–300 Hz or so. Phonation at the fundamental frequency is then filtered by the vocal tract to produce speech. The vocal tract can be modified by changing the shape (dashed lines) of the pharynx, or upper airway, through muscles innervated by cranial nerves IX and X. Movements of the tongue (cranial nerve XII) and lips (not shown, cranial nerve VII) modify the shape of the oral cavity. The position of the uvula, another influence on the shape of the vocal tract, is controlled by muscles of the soft palate, which are innervated by cranial nerve IX.



narrow our pharynx, depress our tongue, and open our lips to say the “ah” sound in “hot.” As these two examples illustrate, the movements involved in language articulation are complex and precise. It is no surprise then that even small lesions in motor areas related to cranial nerves innervating muscles that change the shape of the vocal tract (VII, IX, X, XII) can produce **dysarthria** (see Chapter 10).

SPEECH COMPREHENSION EMPLOYS A RICH INTERPLAY BETWEEN CONTEXT AND ACOUSTIC INFORMATION

Even with perfect articulation, the sounds of speech are not unambiguous. No reliable silence occurs between words or syllables. A single **phoneme**, such as /t/ or /d/, is pronounced differently depending on the phonemes that come before and after. The /d/ sound in the syllables “dee” and “due” differ. In contrast, the sound produced when we say “d” and “b” can be very similar. The ambiguity of phonemes necessitates our spelling out letter codes and names, which have no inherent meaning, with words such as “alpha, bravo, charlie, delta” and so on. Thus, speech is not simply an acoustic version of written language.

Although the sounds of speech do not unambiguously reflect words, we customarily understand speech with high accuracy. In large part, this is because context

A VARIABLE DELAY INTERVENES BETWEEN VISUAL AND AUDITORY INPUTS.

Light travels about one million times as rapidly as sound. Therefore, as a person speaks to you from a meter away, sound reaches you in 3 ms but light reaches you in 3 ns. The interval between light and sound arrival is far greater with larger distances between the speaker and listener, such as occur in a movie theater. Mitigating the effect of this delay, phototransduction depends on a

metabotropic receptor and is far slower than auditory transduction, which depends on ionotropic mechanoelectrical transduction channels. We appear to be somewhat forgiving in the alignment between sound and lip movements, as we understand speech in films, most of which depends on a postproduction process of aligning audio and video tracks.

limits the possible interpretations of what we hear. Our comprehension of spoken language depends on a number of cues beyond the acoustic input conveyed via the cochlea. Aiding our comprehension of communicated content are body language, facial expression including lip movements, and context. For example, we hear “Call me” when a person holds their hand next to their face in the universal sign for a telephone, elevates their eyebrows and says “Hall me.” Even when we rely entirely on acoustic information, context is critical to our understanding of what we hear. We often delay interpretation of one acoustic component until more acoustic components are available to provide additional clues.

Spoken language evolved as an interaction between two people: speaker and listener. The listener carries into the interaction expectations concerning what the speaker may want to communicate. We easily understand the sentence, “Did you eat breakfast yet?” spoken by a significant other, early in the morning, and at home. In contrast, we are unlikely to correctly “hear” the same sentence spoken by a boss, in the afternoon, and at the office. One of the most important clues that we use to decipher the ambiguous sounds of speech is lip reading (see Box 17-18). In a well-known auditory illusion, the **McGurk effect**, an auditory /ba/ combined with a visual /ga/ produces the illusion of having heard /da/. In individuals with hearing loss or in those that rely upon cochlear implants, lip reading is particularly critical to accurate speech interpretation.



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CHAPTER 18

SOMATOSENSATION: FOCUS ON PAIN

SOMATOSENSATION IS AN UMBRELLA TERM FOR VARIED SENSORY PATHWAYS

Somatosensation is a far more varied system than either audition or vision. One striking result of this greater heterogeneity is that no one suffers from a complete absence of somatosensation. We do not even have a word for such a condition. In contrast, both the absence and severe impairment of vision and hearing are relatively common, with almost 1 in 20 people suffering from deafness, severe hearing impairment, blindness, or low vision even with correction. There are two primary reasons for the difference between vision and hearing on one hand and somatosensation on the other. First, light and sound arrive through two portals each, our eyes and ears, whereas somatosensory afferents cover the body surface and canvass the viscera and other deep structures. Second, the transducing pathways for light and sound are limited, so that dysfunction of any of a large number of molecules knocks out function. In contrast, as described below, there are at least a dozen known transduction pathways, and surely more yet to be discovered, involved in somatosensation. Thus, the only condition that renders a person **anesthetic** is a traumatic injury rostral to the sensory trigeminal complex. Although Jean-Dominique Bauby, introduced in the first chapter, had just this injury due to a stroke that left him locked-in, the injury occurs rarely and is survived even less often.

Somatosensory modalities run the gamut from finely discriminated perceptual modalities, such as the sense of touch, to poorly discriminated perceptual modalities such as visceral pain, to modalities that do not reach conscious perception at all, such as blood pressure or oxygen tension. As an example of a finely discriminated form of somatosensation, tactile pathways from our fingertips allow us to discriminate, without looking, glossy from matte paper, burlap from flannel, and flannel from brushed cotton. In contrast, a variety of visceral stimuli such as an overly distended stomach from eating too much, a peptic or duodenal ulcer, gallstones, or appendicitis all elicit essentially the same result: a report of abdominal pain, moaning, and holding the abdomen. *Under normal circumstances, the somatosensory system contributes more to shaping movements than to forming our detailed perception of the world.* Somatosensory input from muscles and joints drives fundamental motor reflexes,

input from our fingertips determines the firmness of our hand grip, and input from the oral cavity determines whether we chew, suck, or swallow. Even acutely painful events, such as stubbing a toe, which are certainly *perceived* are quickly forgotten and thus only briefly contribute to our conscious experience of the world. From this perspective, somatosensation closely resembles the vestibular sense, which is most critical to postural and orienting movements (see Chapter 19). In this regard, somatosensation contrasts sharply with audition and vision, which are so important to our perceptual world.

The role of somatosensation in our perceptual life is radically altered by injury or disease. Damage to peripheral tissues, peripheral nerves, or central pathways of the somatosensory system causes dramatic changes in the perceptual quality of normally unremarkable stimuli. We may feel constant awareness of a body part or an abnormal, and usually bothersome, sensation such as numbness or pins and needles. Positive signs arising from somatosensory dysfunction can be very unpleasant, as is the case with spontaneous feelings of pain or **allodynia**, meaning pain elicited by a normally innocuous stimulus such as a light touch. The experience of allodynia is common and can result from injuries such as a sunburn, open blister, or bruise. Luckily, in these cases, pain is transient and reversible. Unfortunately, some types of persistent pain change the nervous system at several levels and are difficult to reverse. As chronic pain is a common reason for individuals to seek medical help, we concentrate on the mechanisms underlying the transition from acute injury to chronic pain.

As has been emphasized from the first chapter, damage to somatosensory pathways produces positive signs as well as negative ones. Further, it is usually the positive signs that impel individuals to seek medical help. Therefore, our exploration of the mechanisms and pathways involved in touch perception is slanted toward understanding the contribution of the dorsal column-medial lemniscus pathway to the generation of paresthesias. Second, we examine and contrast the properties of superficial and deep pain along with the differences between superficial, escapable pain and deep, inescapable pain. Third, we look in some detail at the peripheral and central changes triggered by acute injury or disease that lead to long-lasting, chronic pain. Finally, endogenous modulation of somatosensation is briefly considered.

CUTANEOUS MECHANORECEPTIVE AFFERENTS RESPOND TO A DIVERSE RANGE OF INNOCUOUS STIMULI

As was introduced in Chapter 9, several types of primary afferents respond to superficial stimuli with different characteristics. Afferents innervating the skin can be divided into two classes, each of which is itself diverse and can be divided into several subclasses. Mechanoreceptors that support the fine discrimination of mechanical stimuli form a class of $A\beta$ fibers. $A\beta$ sensory fibers respond to innocuous mechanical stimuli including light touch, hair movement, and vibration. The second major class of cutaneous afferents are $A\delta$ and C fibers and include nociceptors and thermoreceptors that respond to noxious and innocuous thermal stimuli, respectively. In addition, there are $A\delta$ and C fiber mechanoreceptors

that do not support tactile discrimination but rather contribute to pleasurable and crudely discriminated forms of touch or stroking.

Initially, we focus on A β mechanoreceptive afferents. A β mechanoreceptors are large neurons with large-diameter, well-myelinated axons. Consequently, action potentials are conducted rapidly along the processes of A β afferents (Fig. 18-1A). Mechanoreceptors involved in *perception* fall primarily into two groups:

- Low-threshold mechanoreceptors are excited by touch or skin deformation. Different types of mechanoreceptors are tuned to mechanical stimuli of different temporal frequencies.
- **Pacinian corpuscle** afferents respond to vibration. Note that Pacinian corpuscles are located deep in the hypodermis and yet are so sensitive that they sense superficial vibration over a wide area of the body surface.

Activation of members of one class of afferents is *roughly* aligned with a perceptual modality. For example, vibration excites Pacinian corpuscle afferents and also typically leads to the perception of vibration. Similarly, excitation of a low-threshold mechanoreceptor normally elicits a sensation of touch. Identifying the most typical percepts resulting from strong activation of different classes of somatosensory afferents provides a useful way to learn and think about the basic organization of somatosensory inputs. Yet, this approach is a simplification. In reality, *no single receptor class is dedicated to one percept and no single percept relies on a single receptor class* (see Box 18-1).

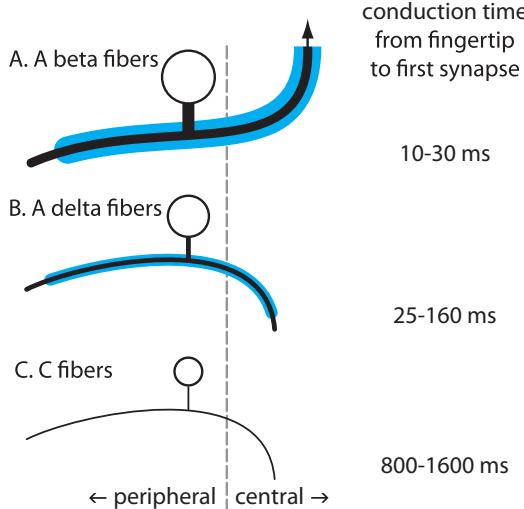


Figure 18-1. A β , A δ , and C fibers differ in the caliber, or width, of their axons (black) and in the amount of myelination surrounding their axons (blue). Note that even the myelinated A fibers lose their myelin at the ends of their processes. As a result of the different caliber axons and myelination, action potentials conduct at different speeds along the three fiber types. In the right hand column are given the approximate times required for an action potential to travel from the fingertip to the first central synapse in a woman of average height. In the case of A β fibers (A), the first synapse is in the dorsal column nuclei (arrow). In the case of A δ and C fibers (B-C), the first synapse is in the dorsal horn. The dotted line shows the edge of the central nervous system.

MOST LOW-THRESHOLD INFORMATION ASCENDS IN THE DORSAL COLUMN-MEDIAL LEMNISCUS PATHWAY

A β sensory afferents carry information about tactile inputs, vibration, and proprioception and conduct action potentials rapidly at speeds of 30–70 m/s. A β afferents enter the spinal cord through the medial portion of the dorsal root (Fig. 18-2), the portion of the root closest to the dorsal column. The axons immediately enter the dorsal column and turn to ascend rostrally. As A β fibers enter at progressively more rostral segments of the spinal cord, they extend the dorsal column laterally. Therefore, axons in the most medial part of the spinal cord carry information that entered in the most caudal segments (see Fig. 9-10). Recall that sensory afferents innervating the perineal region, not the feet, arise from the most caudal dorsal root ganglia and thus enter the spinal cord most caudally and travel most medially (see Fig. 9-6). This topographic arrangement means that in the cervical cord, axons in the most medial parts of the dorsal columns carry information from the perineum. Axons located

WETNESS IS A COMPOUND SENSATION THAT REQUIRES ACTIVITY IN MORE THAN ONE AFFERENT TYPE.

Wetness is a perception that requires activity in two classes of sensory afferent: low-threshold mechanoreceptors and thermoreceptors sensitive to cold. As a result, water at skin temperature does not register as wet. For example, when swimmers enter a heated pool, they are often unable to discriminate the water line by feel alone. The ability to sense wetness is further compromised in competitive swimmers who shave their body hair and therefore receive neither mechanical nor thermal stimulation from entering a heated pool.

The dependence of wetness sensations on both mechanical and thermal input means that tissues not innervated by both thermoreceptors and low-threshold mechanoreceptors cannot support the sensation of wet. Most of our deep tissues, including our viscera, are not innervated by low-threshold mechanoreceptors, such as those innervating skin. For example, our esophagus is innervated by cold thermoreceptors but not by low-threshold mechanoreceptors. Consequently, a cold drink traveling down our esophagus elicits a perception of cold but not of wet. An exception to the general rule that we

cannot sense wetness in deep tissues is our ability to discriminate between gaseous, liquid, and solid contents in the anal canal. Essentially, we sense *phase*—solid, liquid, or gas—by using the compound sensation of wetness derived from inputs from mechanoreceptors and thermoreceptors. In fact, we are able to detect small changes in temperature of less than 1°C within the anal canal.

Detecting the phase of the contents of the anal canal allows us to distinguish between **flatus**, or gas, diarrhea, and stool and to accordingly direct our actions. In fact, we automatically, and regularly, *sample* the contents of the rectum by relaxing the inner anal sphincter to allow rectal contents to enter into the anal canal. When afferents supplying the anal canal are damaged, the sensory arm of the sampling process is damaged, and fecal incontinence can result. Individuals with **idiopathic fecal incontinence** may be unable to detect the small changes in the temperature of sampled contents that normal people detect. Impaired sensory sensitivity within the anal canal, along with muscle weakness, is one of several possible causes of fecal incontinence.

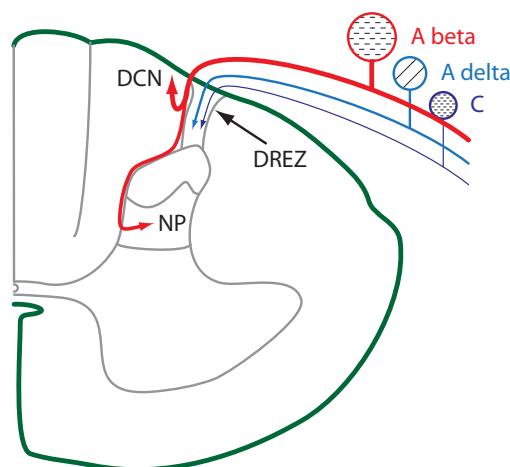


Figure 18-2. A β fibers enter the spinal cord more medially than do A δ and C fibers. A β fibers send their main axon up the ipsilateral dorsal column toward the dorsal column nuclei (DCN). A β fibers also give off collaterals that contact nucleus proprius (NP) neurons. In this way, tactile input carried by A β fibers reaches the dorsal horn. A δ and C fibers enter in the dorsal root entry zone (DREZ), just lateral to the entry point of A β fibers. DREZ lesions have been used to neurosurgically treat intractable pain. Unfortunately, although they provide temporary relief, the relief does not last and is typically replaced by neuropathic deafferentation pain.

in progressively more lateral positions carry information from the feet, distal legs, proximal legs, lower trunk, upper trunk, hands, distal to proximal, shoulders, neck, and back of the head.

Primary afferents travel through the dorsal columns to terminate in the dorsal column nuclei located in the caudal medulla. Thus, large-diameter afferents that innervate the foot extend from a peripheral terminal in the foot to a central terminal in the caudal medulla at the base of the skull. These primary afferents are easily the longest neurons (see Box 18-2) and indeed are the longest cells in the body! Upon reaching the dorsal column nuclei, primary afferents terminate. Dorsal column nuclear cells send an axon across the midline to reach the thalamus. The crossing of axons arising from dorsal column nuclear cells is often referred to as the *sensory decussation*. It is very important to remember that *below the sensory decussation, tactile, vibratory, and proprioceptive information travels on the same side as the stimulus, and above the sensory decussation, this information travels contralateral to the stimulus*. After crossing the midline, the axons of dorsal column nuclear cells travel in the medial lemniscus, a pathway that we followed in our tour through the brainstem (see Chapter 12). The medial lemniscus terminates in the thalamus carrying tactile information from the contralateral body.

Recall that low-threshold touch, vibration, and proprioceptive information from the face and oral cavity terminates in the main sensory nucleus, the trigeminal analog to the dorsal column nuclei. Neurons in the main sensory nucleus project to the medial

Box 18-2

MOST NONTRAUMATIC PERIPHERAL NEUROPATHIES INITIALLY PRODUCE SYMPTOMS IN THE FOOT.

The nerves that extend to the feet are the longest peripheral nerves. Nerve length makes for nerve vulnerability. The vulnerability of long nerves stems from two factors:

- More nerve surface area is exposed to potentially harmful substances.
- Damage to an axon or to its glial wrapping at any one spot disables, or at least greatly impairs function of the entire axon. Therefore, the greater length of nerves innervating the feet is associated with a greater risk of conduction failure or significant slowing.

Because of the vulnerability of long nerves, neuropathies caused by toxins or metabolic disorders primarily affect distal function. One of the most common neuropathies, diabetic neuropathy, is

prevalent in individuals with diabetes mellitus and usually causes symptoms that are restricted to the feet. Since both sensory and motor axons are vulnerable, diabetic neuropathy usually affects all types of nerve fibers: sensory, somatomotor, and autonomic. Thus, a typical case of diabetic neuropathy is an individual with diabetes who complains of pain and abnormal sensations arising from the feet, pain when walking, weakness in the feet and ankles, and sores on the feet that do not heal. Non-symptomatic abnormalities, changes that patients do not complain of, are often present in shorter nerves. For example, individuals may be insensitive to the sensation produced by placing a vibrating tuning fork on either the hands or feet. More information, at more cost, can also be gained from a nerve conduction study. Abnormalities may never develop into problems or may become problematic after further disease progression.

portion of the ventrobasal complex of the thalamus through a pathway very similar to the medial lemniscus, with the exception that the trigeminal dermatome is represented both ipsilaterally and contralaterally.

In sum, somatosensory information from the head reaches the ventral posteromedial nucleus, and somatosensory information from the body terminates in the ventral posterolateral nucleus. Thalamic neurons in both lateral and medial parts of the ventrobasal complex send axons through the posterior limb of the internal capsule that project to the somatotopically organized primary somatosensory cortex (see Fig. 13-10).

LOW-THRESHOLD MECHANORECEPTORS GUIDE GRIP AND OTHER ACTIONS

The somatosensory cortex supports the perception of touch (see Box 15-1). In addition, the dorsal column-medial lemniscus pathway is critical for **stereognosis**. Stereognosis is the process by which we use low-threshold tactile input to detect the size, shape, texture, hardness, and other qualities of an object. Using touch alone, we can distinguish a key from a bobby pin from a pencil from a chopstick and so on. In fact we can distinguish these objects simply by running our fingertips over them. Accurate stereognosis requires information from proprioceptors, as well as from cutaneous mechanoreceptors. To understand why this is so, consider holding a baseball in your hand. The baseball stimulates low-threshold afferents all over the **glabrous**, or smooth and nonhairy, surface of your palm and fingers. Similar tactile information arises when you place your hand flat on a table top or flat on a wall. Yet, we easily distinguish between a baseball, a table top, and a wall. We do so by using proprioceptive information regarding the *position of the hand*. The hand curves around a baseball, is horizontally flat when touching the table top, and vertically flat when positioned against a wall.

We use stereognosis to guide our grip of objects. As objects vary, so do grips. Heavy objects require a firmer grip than light objects. A bottle requires a wider grip than a pencil. In sum, somatosensory information, principally from the dorsal column-medial lemniscus pathway, is used to ensure that a grip is appropriate to both the object and the goal for that object (see Box 18-3).

NOCICEPTION IS THE SENSATION THAT NORMALLY LEADS TO A PERCEPTION OF PAIN

We now turn our attention to pain. Immediately, we have a definitional problem. How do we know what is painful and what is not? The gold standard is a person's subjective verbal report of feeling pain. That gold standard cannot be used for babies and other nonverbal individuals. Nor can

Box 18-3

CLUMSINESS MAY RESULT FROM A FAILURE OF SOMATOSENSORY INFORMATION TO CORRECTLY GUIDE GRIP.

Recall that *neuropathy* is a general term for a disorder involving peripheral nerves (see Chapter 9). Individuals with a neuropathy affecting the hands often complain of dropping things. Motor weakness due to affected motoneuron axons typically contributes to such clumsiness. However, damage to sensory afferents can also contribute to clumsiness by impairing the *sensory guidance* of grip. Faulty information about the size, weight, or slipperiness of an object will result in a correspondingly faulty grip and consequently the dropping of an object. As detailed in Box 18-4, certain neuropathies preferentially affect

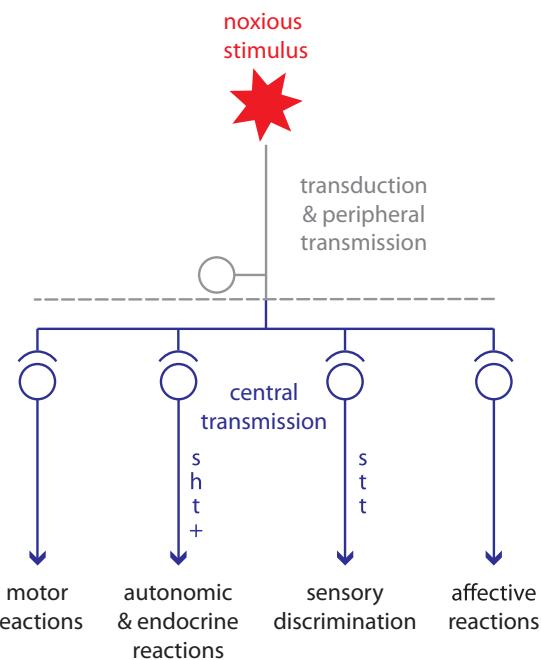
selected populations of peripheral axons such as large, well-myelinated axons or small unmyelinated axons. Afferents that convey information used to recognize body position include low-threshold mechanoreceptors from the skin, as well as joint and muscle afferents. All of these afferents have large, well-myelinated axons that are only slightly smaller in diameter than the axons of motoneurons. Thus, when present in nerves supplying the hands, **large fiber neuropathies**, those that preferentially affect large diameter axons may cause clumsiness through impairment of sensory as well as motor function.

verbal reports be acquired during general anesthesia. Consequently, we use the term **nociception** to refer to the sensory pathway that normally results in a perception of pain. The advantage of the term nociception is that it is noncommittal regarding whether or not the final step, pain perception, occurs. Thus, a noxious stimulus activates nociceptive neurons in nociceptive pathways even in instances when pain perception is blocked. One such condition is opioid analgesia, meaning the relief of pain by an opioid such as morphine.

As introduced in Box 13-20, the experience of pain involves both a discriminative aspect and an affective component. Both components of pain depend on the initial transduction of peripheral stimuli and on transmission from nociceptors to dorsal horn cells. The pathways supporting the discriminative and affective components of pain start to diverge at the point that nociceptive dorsal horn cells project to brainstem and diencephalic targets (Fig. 18-3). As the reader knows, some nociceptive neurons in the superficial dorsal horn send an axon across the midline and into the ventrolateral funiculus to form the spinothalamic tract. The spinothalamic pathway ends in the ventrobasal complex of the thalamus; thalamic neurons in turn project to primary somatosensory cortex where sensory discrimination for pain and temperature occur.

Several additional pathways arise from nociceptive dorsal horn cells. The spinohypothalamic tract conveys nociceptive information to the hypothalamus and may be important in coordinating autonomic and endocrine reactions to pain. Pathways from the dorsal horn that ultimately reach the anterior insula and anterior cingulate are critical to the affective component of pain. Individuals with damage to the anterior insula can sense pain, meaning they can describe its sensory characteristics, but they do not care about it. This condition is known as asymbolia for pain (see Box 13-20). The course of the pathways involved in pain affect is controversial but certainly involves both areas in brainstem and regions of thalamus outside of the ventrobasal complex.

Figure 18-3. Nociceptors are the common entry into pain pathways. However, pain pathways diverge upon entering the central nervous system (dashed line). Nociceptive information important for motor reactions, such as withdrawals and escape, reaches the ventral horn and brainstem. Nociceptive information used for autonomic and endocrine reactions travels through multiple tracts including the spinohypothalamic tract (*sht+*). The spinothalamic tract (*stt*) carries nociceptive information important for sensory discrimination to the somatosensory cortex. Nociceptive information critical to affective, motivational, and emotional responses reach the anterior insula and cingulate cortex through a number of pathways.



In the next few sections, we focus on the transduction and peripheral transmission of pain, processes common to all pain pathways.

SMALL-DIAMETER FIBERS INCLUDE NOCICEPTORS AND THERMORECEPTORS

Nociceptors and thermoreceptors are small-diameter, lightly myelinated A δ and unmyelinated C fibers that conduct action potentials either slowly or very slowly, respectively (Fig. 18-1). We focus on five classes of small diameter fibers that contribute to the perceptions of pain and temperature (see Box 18-4):

- **High-threshold mechanoreceptors** are lightly myelinated A δ fibers that respond to sharp, well-localized mechanical stimuli, such as a needle prick.
- **High-threshold thermoreceptors** are lightly myelinated A δ fibers that respond rapidly to noxious heat.
- **Polymodal nociceptors** are a *heterogeneous class* of unmyelinated C fiber afferents that respond to tissue-damaging stimuli of multiple types: thermal (hot or cold), mechanical, or chemical such as capsaicin, the active ingredient in hot chili peppers.
- **Thermoreceptors** are unmyelinated afferents excited by innocuous cool or innocuous warm temperatures.

LARGE- AND SMALL-DIAMETER SENSORY FIBERS DIFFER IN SIGNIFICANT WAYS THAT ARE KEY TO THEIR INVOLVEMENT IN DIFFERENT DISEASES.

The division between mechanoreceptors and nociceptors is a meaningful biological distinction. Most mechanoreceptors are large-diameter, well-myelinated afferents, whereas nociceptors and thermoreceptors are either very thin, unmyelinated or thin, lightly myelinated afferents. Moreover, the molecules involved in both the function and development of the different afferent classes are distinct. For example, certain growth factors or growth factor receptors are required for the development of unmyelinated and lightly myelinated afferents but not for the development of well-myelinated afferents. Therefore, individuals lacking a subset of these molecules are born with a congenital neuropathy called *hereditary sensory and autonomic neuropathy* (see Box 9-2). The differing molecular signatures of afferent classes also render different afferent types more or less susceptible to various environmental insults. For example, hypoxia, local anesthetics, hyperglycemia, the high glucose levels commonly experienced by diabetics, and chemotherapeutic agents often preferentially affect peripheral axons of a certain diameter.

Sensory afferents are not the only peripheral axons susceptible to dysfunction. Motor axons serving skeletal muscle and autonomic axons can also fall victim to errant development or toxic environments. Recall that among all types of peripheral axons, the axons involved in touch are relatively small in diameter. The largest-diameter axons belong to motoneurons that innervate skeletal muscles and proprioceptive afferents that innervate muscles and joints. Thus, the term *large-fiber neuropathy* refers to neuropathies that affect motoneurons and proprioceptive afferents and therefore have primarily motor consequences. In contrast, **small-fiber neuropathies** may affect any combination of mechanoreceptors, nociceptors, and thermoreceptors. In addition, the motor fibers innervating autonomic targets are unmyelinated and therefore also affected in individuals with small-fiber neuropathy.

The effect of chemotherapeutics on sensory neurons is illustrative. Single chemotherapeutics cause neuropathies at rates up to 30%–40%. Combination regimens may lead to neuropathy in up to 70% of patients treated! For most chemotherapeutic drugs, the development of neuropathy limits the dose and course of treatment. Chemotherapeutics produce toxicity through a variety of mechanisms. Platinum-containing drugs, such as cisplatin, cause peripheral neurons, especially those in the dorsal root ganglion, to reenter the cell cycle and then undergo apoptosis or programmed cell death. Other drugs, such as taxanes, prevent microtubule disassembly and thereby disrupt both anterograde and retrograde axonal transport, leading to a dying back of the peripheral terminal. Most chemotherapy-induced neuropathies produce primarily sensory symptoms by damaging sensory neurons, predominantly the largest sensory neurons, mostly A β fibers. Damage to large, well-myelinated A β sensory fibers results in depressed motor reflexes, which depend on large-diameter muscle and joint afferents, as well as paresthesia, dysesthesia, or frank pain. The latter set of positive sensory signs reflects the most common result of damage to sensory pathways. Neurotoxic damage to motor and autonomic axons also occurs but leads to symptoms more rarely than does sensory neuron damage. Currently, decreasing the dose, frequency, or rate of chemotherapeutic infusions represents the only defense against inducing neuropathy. Although some remission of neuropathic symptoms can occur early on, symptom severity typically stabilizes thereafter. Efforts are now aimed at developing prophylactic adjuvants that, when administered with chemotherapeutic drugs, will protect against the development of a neuropathy. Although no clear success has yet been achieved, these efforts clearly hold great potential and hope.

- **Pruriceptors** include a group of unmyelinated C fiber afferents that respond to histamine, the prototypical itch stimulus. Histamine produces a sensation akin to that of a mosquito bite. Most pruriceptive afferents also respond to at least some forms of noxious stimulation (see Box 18-5).

Small-diameter A δ and C fibers exist that code for modalities other than pain, temperature, or itch. For example, C-fiber mechanoreceptors respond to movements of the downy hair. These afferents may signal a form of crude touch, signaling the presence of a stimulus while not providing much discriminative information.

Most somatosensory afferents are very specific, only responding to one type of stimulus such as warming but not cooling, cooling but not warming, hair-bending but not touch, and so on. Polymodal nociceptors stand in stark contrast to this type of specificity. Polymodal nociceptors are highly nonspecific in their response profile

Box 18-5

LIKE PAIN, ITCH IS AN UNPLEASANT SOMATIC SENSATION.

Itch, or **pruritus**, is defined as a sensation that elicits the desire to scratch. Like pain, the perception of itch is experienced as unpleasant. Itch has additional similarities to pain, including the sensory pathway. Most pruriceptive primary afferents and perhaps all pruriceptive dorsal horn cells also respond to noxious stimulation. Importantly, spinothalamic tract neurons that respond to **pruritic**, or itch-producing, stimuli also respond to noxious stimuli. Thus, at the neuronal level, there is virtually a complete overlap of pruriceptive pathways with nociceptive pathways. This conclusion is confirmed by individuals who received an **anterolateral cordotomy**, a neurosurgical lesion of the ventrolateral white matter of the spinal cord that has been performed to alleviate pain. After an anterolateral cordotomy, individuals sense neither pain nor itch on the contralateral side below the level of the lesion. The strong overlap between itch and pain pathways has led some to consider itch as a form of pain. According to this view, itch is no more different from a sharp, lancinating, cutting pain than is a dull, throbbing, aching pain.

There are also several differences between itch and pain. First and foremost, people recognize these two sensations as definitively different. This counts for a great deal and is arguably the bottom line for some. Second, pain is accompanied by avoidance or withdrawal reactions, and itch is defined by scratching. Third, the production of pain by intense scratching relieves pain. Another example of itch-

pain antagonism is that opioid analgesics that alleviate pain *can cause* itch. Finally, naloxone, an opioid receptor antagonist that antagonizes the pain-relieving effects of morphine, is antipruritic, meaning that it reduces itch sensation.

Itch is a nontrivial clinical issue. Not surprisingly, it is the primary complaint of patients seeking dermatological help. Many patients with itch due to bites, poison ivy, or allergic reactions find relief by taking antihistamines that antagonize the peripheral effects of histamine. However, a portion of the patients who seek medical help for itch have **central itch**, a form of itch that does not depend on a peripheral stimulus, such as a mosquito bite. Since central itch is not caused by a peripheral stimulus, such as the release of histamine, it is also unfortunately unaffected by antihistamines. The causes of central itch are varied. Individuals with hepatic failure often suffer from central itch. The itch produced by opioid administration is also a type of central itch. A case of central itch was the topic of an article in *The New Yorker*. After a bout of herpes zoster (see Box 18-12), a woman developed an unrelenting itch. The itch was so imperative that she scratched all the way through her skull and dura. Although this outcome is rare, perhaps even singular, the take-home message is that itch can be a significant clinical problem.

Gawande, A. The itch. *The New Yorker*, June 30, 2008.

as they respond similarly to noxious heat or to cutting the skin or pinching. Yet, nociceptors are specific enough to serve a protective purpose. In other words, regardless of the specifics, any stimulus that causes tissue damage or is likely to do so imminently activates nociceptors. Thus, *nociceptors are specific to physical injury or the threat thereof*. Befitting this specificity, nociceptor activation leads to protective reactions.

DIFFERENT SPEEDS OF ACTION POTENTIAL CONDUCTION UNDERLIE FIRST AND SECOND PAIN

Since action potentials conduct at very different speeds in A δ and C fibers, the perceptions initiated by activity in these two fiber types occur at different times (Fig. 18-1). Consider that a woman of average height steps on a thorn with a bare foot. The thorn will excite both high-threshold A δ fiber mechanoreceptors and C fiber polymodal nociceptors. Since the high-threshold mechanoreceptors have lightly myelinated axons, with conduction velocities of 5–30 m/s, the message that the thorn has impaled the foot will reach the spinal cord in 30–200 ms. In contrast, the unmyelinated axons of polymodal nociceptors conduct action potentials at a far slower rate, 0.5–1 m/s. Consequently, input from polymodal nociceptors takes 1–2 seconds to reach the spinal cord from the foot. The delay between 200 ms and 1 or 2 seconds is perceptible and forms the basis for **first pain** and **second pain**. In general, first pain causes a fast, sharp, well-localized sensation, whereas second pain causes a less well-defined aching or burning pain. The sensations of sharp and shooting versus aching and burning pain roughly reflect the perceptual consequences of A δ or C fiber activation, respectively.

DEEP PAIN IS POORLY LOCATED IN SPACE AND TIME

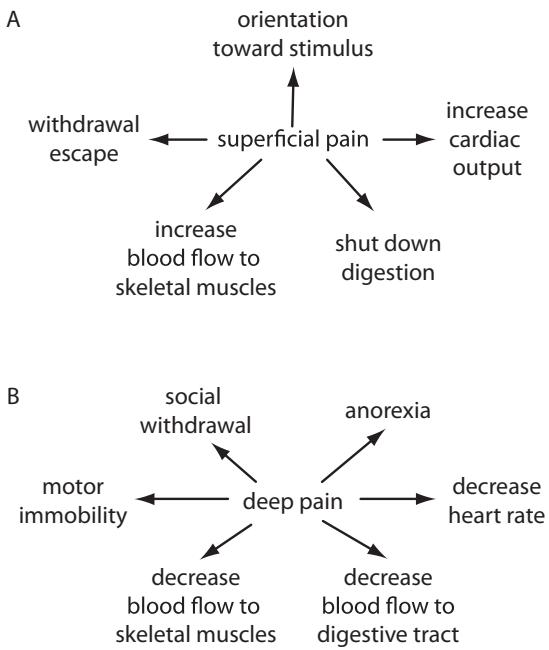
Sir Thomas Lewis was an early 20th-century cardiologist who first described interactions between pain afferents and the peripheral circulation. Although recognized today mostly for his vast contributions to cardiology, Lewis' work on pain remains highly influential today. Lewis lamented that we use the same word, *pain*, to refer to all varieties of pain, which in fact differ extensively from each other. This semantic sloppiness is most evident when we contrast deep pain from superficial pain. Superficial injuries such as a burn, scratch, or a mosquito bite, elicit an acute perception of pain (or itch in the latter case). We even sense the landing of a mosquito or fly on our arm or the moist track of a drip of sweat. In marked contrast to our ability to discriminate, in place and time, superficial stimuli, we are horrible at detecting and describing deep somatic stimuli.

Consider the striking differences between a paper cut and a penetrating injury. As everyone knows, paper cuts are peculiarly distracting, demanding our attention

even when very small. Contrast the paper-cut experience with the experience of individuals who have been stabbed or shot, many of whom first become aware of their injury because of a feeling of warmth on the skin not because of wounded deep tissue. Remarkably, there have been several instances in which a nail gun has backfired, driving a nail into the person rather than into the targeted object. In one case, a man immediately sought medical assistance because his cheek, where the nail penetrated, hurt. After having his cheek sewed up, the man went about his business until a week later when he visited a dentist for a toothache. The dentist took an x-ray that revealed that a nail had shot through the man's teeth and jaw and was now lodged in his frontal cortex. Note that the injured man did not all of a sudden become aware of the nail in his head or the hole in his tooth and jaw. Rather, the man complained of a toothache, a completely inaccurate depiction of the problem reflective of our greater sensitivity to persistent deep pain, borne of infection and the like, than to acute deep pain.

The contrast between our exquisite sensitivity to the smallest cutaneous stimulus and our incredible insensitivity to severely damaging deep stimuli corresponds to the contrasting behavioral strategies used in reaction to the two types of stimuli. Superficial pain perceptions, arising primarily from the skin, signal potential danger and serve as a call to action (Fig. 18-4). Superficial damage is *escapable* and calls for immediate action. In marked contrast, there are a limited number of deep stimuli that we can do something about. We can void when our bladder or colon fills, and we can vomit when we feel nauseated. Outside of these instances, internal events are essentially *inescapable*. We are stuck with deep pain or at least we have evolved as animals that are stuck with deep pain. Modern medicine may provide us with treatment options in many cases, but our nervous system has not evolved to take advantage of this recent development. Like other animals, we react to deep tissue damage by inactivity and a retreat from social interactions, until sufficient recuperation or death occurs. Using this framework, we can understand persistent pain as a form of inescapable pain. Indeed, animals, including humans, react to persistent pain as we do to deep pain—with social retreat and quiet immobility.

Figure 18-4. A: Superficial pain is a call to action. The motor responses to superficial pain include withdrawing from a noxious stimulus, orienting toward the noxious stimulus, and escaping from the situation. The motor activity elicited by superficial pain is supported by increased cardiac output and increased blood flow to skeletal muscles. B: Deep pain is inescapable. Animals, including humans, respond to deep pain by becoming immobile, withdrawing from social interactions, and not eating (anorexia). Cardiac output is decreased, and resources are shifted away from growth and toward the immune system.



NORMALLY, WE DO NOT PERCEIVE THE CONDITION OF OUR VISCERA

Normally, we are not aware of our viscera. We do not perceive blood pulsing through vessels, urine traveling through the ureter, or the expansion of alveoli accompanying every sigh. We can sense distension of some of the hollow viscera, such as the colon, bladder, and even stomach. Yet, even this sensation is very crude. Although the uncomfortable sensation of a distended stomach is indicative of having eaten far too much, we cannot perceive small differences in visceral distension. We cannot, for example, perceive the difference in stomach distension after having eaten two or three slices of apple.

Although the hollow viscera support nonpainful sensations such as urgency, the nonhollow viscera and other deep structures only support a perception of pain. In other words, we do not feel tickle or pressure or warmth or coolness from our pancreas or our dura; we either feel nothing or we feel pain. Several visceral conditions can give rise to a perception of pain:

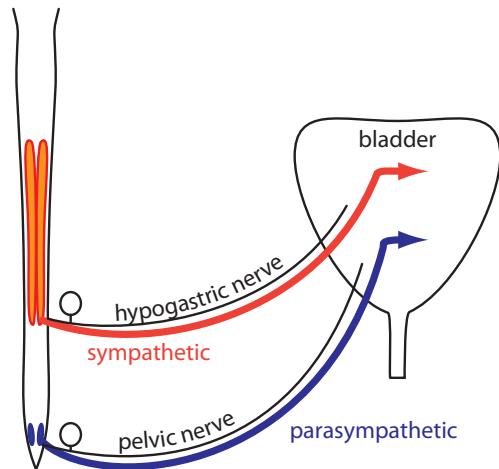
- *Excessive distension:* Failing to empty the bladder or colon can result in distension of these hollow viscera. This produces an acute perception of visceral pain.
- *Inflammation:* Inflammation of any viscera can produce a chronic feeling of pain. Examples include pericarditis, colitis, and appendicitis.
- *Frank tissue damage:* When the viscera is damaged by a disease process, as occurs with a peptic or duodenal ulcer, pain results.
- *Occlusion:* Occlusion of a blood vessel, such as occurs in sickle cell anemia, or a channel such as the ureter, as occurs in kidney stones, is painful.

Thus, the viscera normally give rise to either no sensation or to feelings of fullness in the case of some hollow organs. Yet, when any of the viscera are diseased or damaged, pain can result. The afferents responsible for these very different perceptual conditions are quite different from the complement of cutaneous afferents described above.

VISCERAL AFFERENTS DIFFER SUBSTANTIALLY FROM CUTANEOUS AFFERENTS

Most viscera are innervated by two different nerves. For example thoracic dorsal root ganglion cells reach the bladder through the hypogastric nerve while sacral dorsal root ganglion cells reach the bladder through the pelvic nerve (Fig. 18-5). The bulk of the fibers in the hypogastric nerve are sympathetic fibers destined for pelvic viscera, whereas the bulk of fibers in the pelvic nerve are fibers destined for pelvic parasympathetic ganglia. For this reason, the afferents

Figure 18-5. Primary afferents travel along with sympathetic and parasympathetic nerves. In the example illustrated, the bladder receives sympathetic innervation from the thoracic cord by the hypogastric nerve and parasympathetic innervation from the sacral cord via the pelvic nerve. Both of these nerves also contain the axons of dorsal root ganglion cells from the corresponding level of the spinal cord. Since the thoracic afferents travel with sympathetic efferents, they are sometimes termed *sympathetic afferents*. Similarly, as the sacral afferents travel with parasympathetic efferents, they are sometimes termed *parasympathetic afferents*.



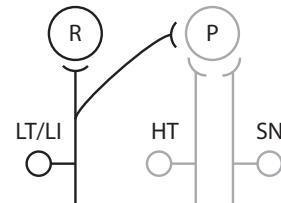
in the hypogastric nerve are sometimes referred to as *sympathetic afferents* and those in the pelvic nerve as *parasympathetic afferents*. These terms have utility. Yet, it is important to remember that all of these afferents have their cell bodies in dorsal root ganglia.

Visceral afferents come in two varieties that roughly align to the sympathetic–parasympathetic division described above. Low-threshold afferents traveling in parasympathetic nerves respond to low-intensity stimulation and are critical to the normal function of the viscera (Fig. 18-6). Information about small changes in the state of the target viscera is carried through these low-threshold afferents to autonomic efferent pathways that maintain homeostasis. Neither the

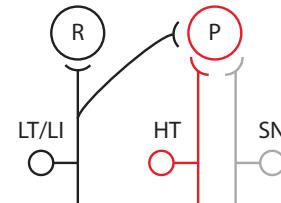
Figure 18-6. **A:** Under normal conditions, in the absence of visceral pain, low-threshold afferents (LT/LI) respond to low intensity stimuli. The responses of low-threshold afferents drive neurons involved in visceral reflex control (R). Input from low-threshold afferents also reaches neurons that project to pathways that ultimately result in perception (P). However, the input from low-threshold afferents is normally insufficient to excite perception-related neurons. **B:** A brief noxious stimulus excites high-threshold visceral nociceptors (HT), which in turn leads to the excitation of perception-related neurons. The result of this activity is acute visceral pain. **C:** After inflammation and central sensitization, silent nociceptors (SN) start to fire spontaneously. The increase in activity in both high-threshold visceral nociceptors and silent nociceptors sensitizes the perception-related pathway. As a result, low-threshold input excites the perception-related pathway. The result is that normal visceral sensations important for homeostasis are now perceived as painful.

Modified from Cervero, F., and Janig, W. Visceral nociceptors: A new world order. *Trends Neurosci* 24:374–78, 1992, with permission of the publisher, Elsevier.

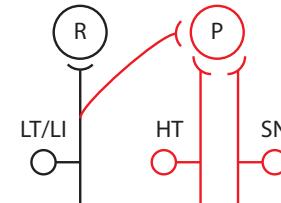
A. Normal conditions: no pain



B. Brief noxious stimulation: acute pain



C. Inflammation and central sensitization: chronic pain



low-threshold visceral information nor the automatic adjustments to visceral function reaches consciousness or contributes to perception. In contrast, afferents traveling in sympathetic nerves have high thresholds for activation and thus function as nociceptors that are only activated by injurious stimuli. The excitation of sympathetic afferents leads to a brief perception of acute visceral pain. Finally, viscera are innervated by **silent nociceptors**. As their name suggests, silent nociceptors are normally silent, neither spontaneously active nor responsive to any natural stimuli. However, in response to an inflammatory stimulus, silent nociceptors become active. When visceral silent nociceptors are sensitized by inflammation, peripheral and central nociceptive pathways are altered (more on this below). As a result, low-intensity visceral input, which normally contributes to visceral reflexes but not to perception, now contributes to perception, leading to a persistent perception of visceral pain (Fig. 18-6C).

SPECIFIC TRANSDUCTION MOLECULES CONFER AFFERENTS WITH PARTICULAR RESPONSE PROFILES

The task of transducing the variety of somatosensory stimuli to which we are sensitive is accomplished by a variety of transduction molecules that are present in somatosensory afferents. Instead of there being one transduction molecule—rhodopsin and the mechanoelectrical transduction channel in the case of light and sound, respectively—a number of receptors are capable of transducing somatosensory stimuli. Each receptor responds to some subset of somatosensory stimuli.

Many of the channels involved in somatosensory transduction that have been identified to date belong to a family of ionotropic channels called transient receptor potential or TRP channels (see Box 8-1). Transient receptor potential channels may be sensitive to (1) temperature, (2) mechanical stimulation, or (3) chemical substances such as camphor, menthol, or capsaicin. Moreover, most of the TRP channels involved in somatosensation respond to at least two stimulus types, and some respond to all three stimulus types. Transient receptor potential channels can thus be considered the perfect molecular substrate for neurons that respond to multiple stimulus modalities. Fittingly, polymodal nociceptors contain one or more TRP channels.

At least nine TRP channel subtypes respond to temperature within differing but overlapping ranges. The task of responding to the normal range of environmental and internal temperatures is divided up between types of TRP channels, so that the entire complement of TRP receptors can support sensations of cold, cool, warm, and hot. For example, one TRP channel subtype, **TRPV1**, is critical to sensing mildly to moderately noxious heat, whereas another transduces intensely noxious heat, and still another member of the TRP family of channels opens at temperatures that are normally perceived as warm. **TRPM8** channels respond to temperatures normally perceived as cool, whereas **TRPA1** channels respond to temperatures normally perceived as cold.

As mentioned above, TRP channels typically respond to more than one type of stimulus. For example, TRPA1 channels respond to cold and also to irritants such as acrolein and other components of smoke, smog, and exhaust. In fact, TRPA1 receptors are activated by chemicals that can covalently bind to cysteine, a varied group that includes nicotine, formaldehyde, and the active ingredients in mustard, wasabi, garlic, and cinnamon, as well as many air pollutants (see Box 18-6). TRPA1 also opens in response to reactive oxygen species, such as hydrogen peroxide, which are produced by cells in oxidative stress.

The TRPV1 channel, which is activated by heat, also opens in response to capsaicin, the ingredient responsible for the spicy hot sensation produced by chili peppers (see Box 18-7). TRP channels are also strongly modulated by a number of substances. For example, protons modify the responses of TRPV1 channels to

Box 18-6

ENVIRONMENTAL IRRITANTS CAUSE INFLAMMATION OF THE AIRWAYS, WHICH OFTEN LEADS TO PULMONARY DISEASE SUCH AS ASTHMA.

TRPA1 and TRPV1 are contained in sensory afferents that innervate the entire length of the airways from nose to lungs, including the nasal mucosa, pharynx, glottis, trachea and bronchi. Activation of these transient receptor potential (TRP) channels elicits an immediate protective reaction, coughing, and also suppresses breathing, which in turn decreases exposure to airborne irritants. We can view the airways as the lungs' "skin," their exposed and superficial barrier from the outside world. In this same vein, coughing, in reaction to airborne irritants, can be thought of as a protective withdrawal, essentially the lungs' version of yanking your hand away from the hot fire.

Acute exposure to agonists at TRPA1 and TRPV1 receptors is effectively countered by coughing and brief episodes of **apnea**, or not breathing. However, the protective effect of coughing goes awry in the face of chronic exposure to irritants. Chronic exposure to pollution, smoke, as well as products of oxidative stress, such as hydrogen peroxide and other reactive oxygen species, causes repeated activation of the TRP channels found in airway afferents. Chronic activation of sensory afferents, in turn, causes a hypersensitivity to airborne irritants through mechanisms analogous to those implicated in the pathogenesis of persistent pain syndromes. The end result is a decreased threshold for coughing, so that

frequent coughing becomes pathological rather than protective. Additional signs of pulmonary disease are airway inflammation, bronchoconstriction, and excessive mucus production, all of which contribute to the primary symptoms of coughing and **dyspnea**, or shortness of breath.

The incidence of **asthma**, **chronic obstructive pulmonary disease**, and **reactive airway dysfunction syndrome** have all greatly increased, particularly in industrialized and polluted regions. The inflammation and sensory afferent hypersensitivity caused by chronic exposure to airborne irritants likely mediates this recent increase in pulmonary diseases. This perspective allows us to understand why certain compounds or environments exacerbate breathing problems. For example, cold, below about 15°C, activates TRPA1 receptors and worsens asthmatic symptoms. Similarly, hypochlorite, the volatile agent arising from chlorinated pools and disinfectants such as bleach, activates TRPA1 receptors and greatly exacerbates asthma. Less well appreciated agonists at the TRPA1 receptor include volatile compounds from cinnamon, wasabi, garlic, onions, and mustard. The critical importance of TRP channels in general and TRPA1, in particular, to pulmonary disease has led to efforts to develop TRP receptor antagonists into novel therapeutics for asthma and other pulmonary diseases.

CAPSAICIN PRODUCES A BURNING SENSATION THAT WE INNATELY AVOID.

TRPV1 is often referred to as the **capsaicin receptor**. TRPV1 is present in trigeminal afferents that innervate the oral cavity of humans and most other mammals. When we eat hot chili peppers, the burning sensation that we feel is due to capsaicin's actions on the TRPV1 receptor. Mammals with the TRPV1 receptor find capsaicin innately aversive, meaning that virtually all mammals will take one taste of capsaicin and then avoid it forever more. The preference

for capsaicin and other hot substances expressed by some humans is an example of a *learned taste preference*. The biology of the TRPV1 receptor has led to a common defense against backyard squirrels gobbling up food intended for songbirds. Since birds do not have a TRPV1 receptor, capsaicin has been added to some bird-feed mixtures. The birds do not notice and happily eat the food offered. On the other hand, squirrels will avoid bird food laced with capsaicin.

temperature and menthol similarly modulates TRPM8 channel responses. In the latter case, menthol raises the threshold for temperature activation of TRPM8 channels, so that a higher temperature is capable of opening the channel. The perceptual result of this is that warmer temperatures are perceived as cool.

The responses of TRP channels to multiple stimuli indicative of tissue damage reflect the diversity of injurious stimuli, as well as the singular meaning of such damage. In other words, *TRP channels respond to several types of damaging stimuli without distinguishing between the properties of the different stimuli*. Thus, TRP channels are the quintessential nociceptive receptor type—a jack-of-all-trades, or at least of-many-trades, an injury-in-any-form-sensing molecule. A further expansion of the injury-sensing repertoire of single nociceptors arises from the multiple TRP channels present within individual neurons.

Many additional transducing molecules, outside of the TRP channel family, contribute to nociception, some of which have been identified and a number of which assuredly have not. Most notably, **acid-sensing ion channels**, or **ASICs**, are ionotropic channels activated by protons, which accumulate extracellularly during injuries such as ischemia, and also after tissue-damaging mechanical stimulation.

NOCICEPTORS ARE RESPONSIBLE FOR MUCH OF THE INFLAMMATION RESULTING FROM TISSUE DAMAGE

An important distinction cuts across the functional classes of nociceptors outlined above. Most A δ and C fiber afferents contain neuropeptides that play important roles in normal everyday function and in the response to injury. Small-diameter afferents that contain neuropeptides are typically referred to as *peptidergic afferents*. The minority of A δ and C fiber afferents that do not contain peptides are termed *nonpeptidergic afferents*. As a rule, A β fiber afferents do not

contain neuropeptides and are nonpeptidergic. The importance of this distinction will become evident below.

Dorsal root ganglion neurons are peculiar in that they send out a single process that bifurcates into two long processes, one of which extends to a peripheral target and one of which enters the central nervous system. The process that extends peripherally is dendrite-like in that it receives input but axon-like in that it conducts action potentials. In the case of many primary somatosensory afferents including high-threshold mechanoreceptors and polymodal nociceptors, the peripheral process ends in a spray of terminals connected by short branches to the main or parent process (Fig. 18-7A). The receptive field of somatosensory afferents with such a spray of terminals consists of a series of punctate spots (see Fig. 15-4).

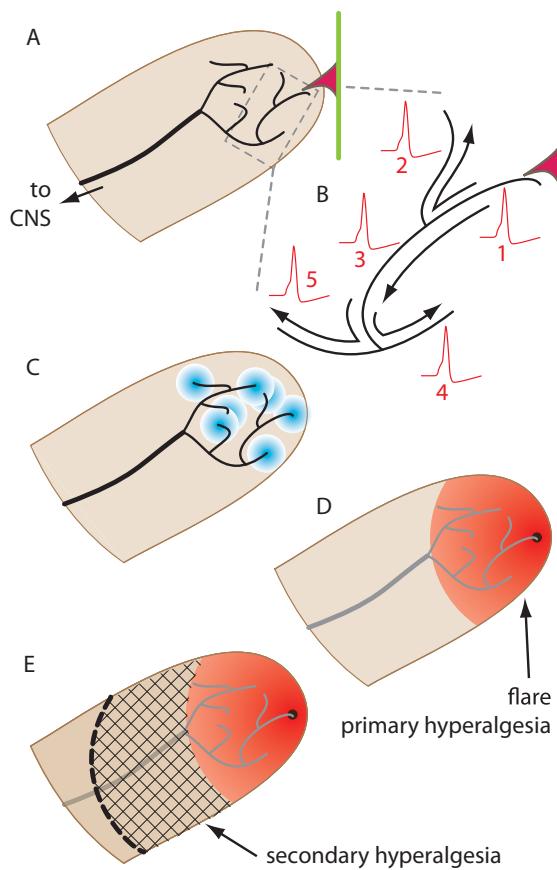


Figure 18-7. Peptidergic nociceptors end in a spray of terminals. When a thorn stimulates one ending of a nociceptor (A), an action potential is elicited. B: The initial action potential (1) is conducted back to the first branch point. At each branch point, the action potential invades the sister branch (2, 4) as well as the parent fiber (3, 5). C: When an action potential reaches the ending of a peptidergic nociceptor, peptides including substance P, calcitonin-gene related peptide (CGRP), and neurokinin A are released into the periphery (blue spheres). D: CGRP released from nociceptors causes a secondary vasodilation or flare. In addition, the inflammatory soup that is triggered by the release of neuropeptides sensitizes nociceptors, causing primary hyperalgesia in the flare zone. E: The barrage of nociceptor activity initiates central sensitization, which results in a zone of secondary hyperalgesia.

The sensory function of primary afferents is served by action potentials that travel from the peripheral receptive field to a terminal in the dorsal horn where neurotransmitter is released. However, recall from Chapter 5 that action potentials travel in one direction only because of the refractory period. Therefore, when an action potential arrives at a branch point, it *invades*, or travels down, the parent axon but also can invade the sister branch (Fig. 18-7B). In this way, an action potential at one branch ending can reach all of the other branch endings of the parent neuron, a process that is termed the **axon reflex**.

The axon reflex has important consequences in the case of peptidergic nociceptors. An injury such as a sting, mechanical injury, or sunburn breaks open blood vessels and cells and also activates nociceptors. The direct damage is localized and forms a small red spot, often referred to as a **bleb**. If this bleb, which occurs without any contribution from nociceptors, were all that occurred, we simply would not care about bee stings, sunburns, scrapes, and cuts. The reason that we do care about initially mild injuries, the reason indeed that they are injuries rather than passing nothings, is *because* of the amplification of the injury set in motion by peptidergic nociceptors.

The amplification of tissue damage by nociceptors is termed **neurogenic inflammation**, and it occurs because of (1) the axon reflex and (2) the peptides released by nociceptors. We now go through this process step by step. When an action potential occurs at the ending of a peptidergic nociceptor, neurotransmitters including neuropeptides are released *from* the nociceptor and *into the periphery* (Fig. 18-7C). The neuropeptides substance P, **neurokinin A**, and calcitonin gene-related peptide (CGRP) are particularly important. Each of these peptides has one or more important effects (Fig. 18-8):

- CGRP causes the vasodilation of blood vessels. This causes the **flare** or **secondary vasodilation** (the primary vasodilation is the bleb) that *extends* around the bleb marking the site of an injury (Fig. 18-7D). The range of the flare represents the territory under the influence of all of the terminals belonging to stimulated nociceptors. Thus, through the axon reflex, action potentials invade all of the branches of all of the nociceptors activated by an injury. Neuropeptides are released from branch

endings and the released CGRP in turn dilates all nearby blood vessels, resulting in the flare.

- Substance P and neurokinin A render blood vessels more permeable, so that plasma leaks out of the vessels and into the local tissue. The leaking of plasma from blood vessels, termed **plasma extravasation**, results in swelling or **edema** (see Box 18-8). Among the proteins that leak out of the now highly permeable venules is a potent pain-producing, or **algesic**, peptide called **bradykinin**.
- Substance P stimulates mast cells, located deep in the dermis, to **degranulate**, meaning that the chemical contents of secretory vesicles or granules in the mast cells are released. As a result, histamine, serotonin, prostaglandins, and nitric oxide join the mix of chemicals present in injured skin.
- Substance P promotes the movement of white blood cells from blood vessels into damaged tissue and the resulting release of a dizzying array of signaling molecules including cytokines, prostaglandins, thromboxanes, leukotrienes, and nitric oxide.

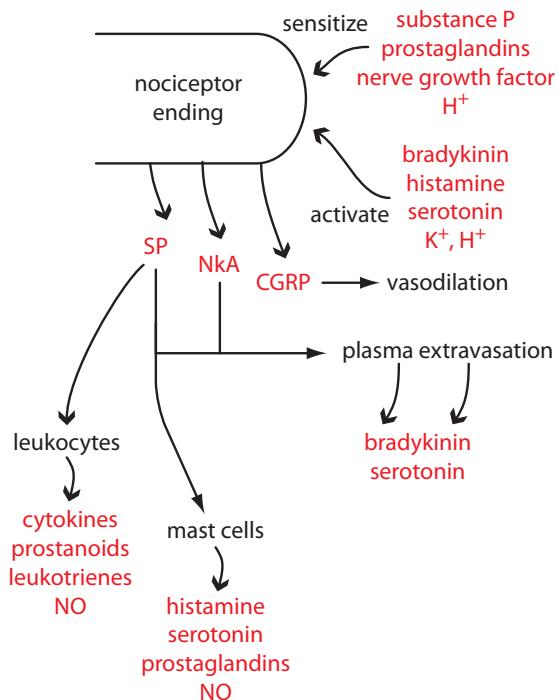


Figure 18-8. A few of the pathways important in neurogenic inflammation and primary hyperalgesia are illustrated. Nociceptors release substance P (SP), neurokinin A (NkA), and calcitonin-gene related peptide (CGRP). CGRP elicits vasodilation, whereas substance P and neurokinin A trigger plasma extravasation of a number of compounds, including bradykinin and serotonin. Substance P also promotes the recruitment of leukocytes into the damaged tissue and the degranulation of leukocytes and mast cells. Substances released from leukocytes and mast cells add to the inflammatory soup (red) within the damaged tissue. Substances present in inflamed tissue increase the activity and sensitivity of nociceptors. The perceptual consequence is primary hyperalgesia.

The end result of the initial injury and subsequent neurogenic inflammatory reaction is that damaged tissue is bathed in an **inflammatory soup** (Fig. 18-8). This inflammatory soup serves an organism well in two respects. First, the soup promotes the immune fight against infection and thus is anti-infective. Second, the inflammatory soup produces peripheral sensitization that reduces use of the body part. Less use of an injured body part means that there is less chance for reinjury.

Both the spontaneous activity and the sensitivity of nociceptors throughout the region of the inflammatory environment, outlined by the extent of the flare, are dramatically increased. One of the most important components of inflammatory soup that contributes to the sensitization of polymodal nociceptors is the class of **prostanoids**, which include prostaglandins, prostacyclins, and thromboxanes. The synthesis of prostanoids is the target of nonsteroidal anti-inflammatory medicines such as **acetylsalicylic acid** or aspirin (see Box 18-9). The increase in activity and sensitivity among regional nociceptors is a process termed **peripheral sensitization**. Thus, after **sensitization**, nociceptors:

- Are active spontaneously
- Respond to stimulation that ordinarily does not evoke a perception of pain
- Have a heightened response to noxious stimulation

The behavioral result of peripheral sensitization is **primary hyperalgesia**. Stimulation in the flare area around a sting, burn, or wound produces a perception of far greater pain than normal. Although termed **hyperalgesia**, primary hyperalgesia also involves spontaneous

Box 18-8

THE TRIPLE RESPONSE INCLUDES HEAT, FLARE, AND WHEAL.

Thomas Lewis described the changes in microcirculation that occur at and around a region of cutaneous damage as the **triple response**. In his original account, he described that in response to a firm stroke, a line of red appears. This red line is equivalent to primary vasodilation, a signature of direct tissue damage. The area on either side of the line then develops a flare, or secondary vasodilation in modern parlance. This flare renders the skin both red and hot. Within minutes, a wheal, a raised region signifying an edematous reaction, develops due in part to plasma extravasation.

pain and allodynia. As is familiar to everyone from experiences with cuts, scrapes, stings, burns, and the like, even the light touch of an inflamed area can elicit pain; the perception of pain in response to innocuous stimulation is called *allodynia*.

NOCICEPTORS NORMALLY SERVE AN EFFERENT FUNCTION

The axon reflex is a remarkable physiological trick that allows nociceptors to serve an *efferent* function that ultimately recruits immune and circulatory resources to the site of an injury and also to the surrounding region, which may be particularly vulnerable to damage. **Hyperemia**, or increased blood flow, may aid in clearing tissue of harmful substances. Certain components of the inflammatory soup actually *protect* targeted tissue. Nociceptor activation and sensitization leads to an exaggerated pain response which ensures that an injured body part is not used. All together then, at least some of the neurogenic reactions to tissue damage are advantageous in the face of acute injury as they speed healing and prevent further damage.

In an example of natural parsimony, the efferent functionality of nociceptors serves a protective role in the *absence* of an injury. Under normal, everyday conditions, peptidergic nociceptors promote the health of innervated tissues. Thus, nociceptors that may never signal tissue damage, even over the course of a human lifetime, are responsible for exerting *trophic* effects that maintain the well-being of innervated tissues. In fact, *most nociceptors, most of the time, are more active as trophic influences on target tissues than as sensors of pain-producing stimuli*. Body tissues as diverse as skin, hair follicles, tooth pulp, tympanic membrane, dura, vertebral column, joints, and viscera all receive nociceptor innervation. In the absence of nociceptors, obvious changes in hair and nail growth, skin, bone, and cartilage abound. Further, the response of tissue to injury, *wound healing*, is greatly retarded in the absence of nociceptor innervation (see Box 18-10).

CHRONIC INFLAMMATION ACTIVATES A CLASS OF SILENT NOCICEPTORS

Although unpleasant to experience, acute pain and inflammation in response to an injury are beneficial as they promote healing and tissue recovery. In contrast, chronic inflammation has negative consequences for the innervated tissue and may even exacerbate damage to the target tissue. Several factors contribute to the hyperalgesia and tissue damage that accompany chronic inflammation. There is a class of silent nociceptors which, as introduced above, are inactive and unresponsive until triggered by damage to become spontaneously active and responsive. An inflammatory stimulus renders these afferents responsive to even innocuous stimulation of the innervated tissue. Silent nociceptors

Box 18-9

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS SLOW AND DIMINISH PRIMARY HYPERALGESIA.

Nonsteroidal anti-inflammatory drugs, commonly abbreviated as NSAIDs, such as acetaminophen, ibuprofen, naproxen, and acetylsalicylic acid, have effects on many physiological functions. Critical to their analgesic, or pain-relieving, effect, NSAIDs block the synthesis of prostanoids—prostaglandins, prostacyclins, and thromboxanes—by inhibiting cyclooxygenase enzymes. Since prostanoids have short half-lives, in the seconds to minutes range, inhibiting their synthesis quickly reduces the amount of the prostanoids even in inflamed tissue. The reduction in prostanoids reduces both inflammation and the pain that normally accompanies inflammation. Since there are plenty of inflammatory mediators within damaged tissue, it is understandable that the inhibition of prostanoid synthesis alone does not abolish inflammatory pain. It is, in fact, a testament to the power of prostanoid-mediated nociceptor sensitization that NSAIDs provide as much pain relief as they do.

are classified as nociceptors because their activity boosts nociceptive transmission in the central nervous system. Silent nociceptors provide one avenue through which innocuous stimuli gain entrance to nociceptive pathways with the ultimate result that a perception of pain is elicited by innocuous and noxious stimuli alike. Thus, silent nociceptors bump up the pain experienced from damaged tissue.

The inflammatory response is most beneficial when it operates as a quick fix, a response that peaks and subsides rapidly. When inflammation persists, tissue damage can be exacerbated as occurs in at least some forms of **arthritis**, a heterogeneous group of conditions involving joint damage (see Box 18-11). The mechanisms by which chronic inflammation damages tissue are not well worked out. However, it appears that, while many components of inflammatory soup protect and maintain tissue health, some are harmful to tissue health, at least when present over an extended period of time.

MULTIPLE SOMATOSENSORY INPUTS CONVERGE ON NOCICEPTIVE DORSAL HORN CELLS

Each nociceptive dorsal horn cell receives input from many nociceptors. The convergence of numerous individual nociceptors of one type, such as A δ high-threshold mechanoreceptors, is the basis of a central neuron's receptive field that is smoother and larger than the receptive field of a primary afferent. Furthermore, multiple types of primary afferents converge upon single dorsal horn cells. Many nociceptive cells receive input from thermoreceptive and pruriceptive afferents. Some dorsal horn cells that respond to noxious stimulation even receive input from A β mechanoreceptors. The extent and significance of the convergence of nociceptive and non-nociceptive input onto some dorsal horn cells are not entirely clear. Yet, one outcome of the arrangement is the possibility of facile modulation of dorsal horn neurons. For example, a dorsal horn neuron that receives inputs from multiple afferent types may respond preferentially to one type of input normally and to a different type of input under different conditions, such as after injury.

A BARRAGE OF NOCICEPTOR INPUT CHANGES THE PHYSIOLOGICAL PROPERTIES OF NOCICEPTIVE DORSAL HORN CELLS

Tissue damage has long-lasting effects on nociceptive dorsal horn neurons through a process termed **central sensitization**. Central sensitization leads to an increase in spontaneous activity and to greatly augmented

Box 18-10

A DEFICIT IN THE EFFERENT FUNCTION OF SENSORY NEURONS CONTRIBUTES TO THE PATHOLOGY OF SKIN ULCERATIONS IN PATIENTS WITH DIABETES.

Without the trophic influences of nociceptor innervation, target tissues become less healthy and less resilient in the face of injury. For example, individuals with peripheral nerve damage often have thickened skin and nails. Without nociceptors, wound healing can be very slow. Diabetic individuals have a reduced density of cutaneous nerve terminals and exhibit decreased neurogenic inflammation. Without the protection of a normal complement of nociceptors, the skin of diabetics is prone to ulceration. Further, without nociceptors to recruit immune cells to damaged tissue, an ulcer that develops in a diabetic individual is more easily infected and less easily healed.

responses to all afferent input, non-nociceptive and nociceptive alike. The behavioral correlates of these changes are familiar by now: spontaneous pain, hyperalgesia, and allodynia. The hyperalgesia involved is termed **secondary hyperalgesia** to distinguish it from primary hyperalgesia, which depends on peripheral mechanisms as explained above. Secondary hyperalgesia involves a large region, expanding well beyond the region of peripheral damage, of heightened sensitivity to somatosensory stimulation (Fig. 18-7E).

Central sensitization can be initiated by a barrage of nociceptor activity, the type of activity that normally occurs in response to severe tissue damage. Central sensitization also occurs after nerve injury or persistent inflammation. The high-intensity afferent input depolarizes dorsal horn cells enough to relieve the magnesium block of postsynaptic N-methyl-D-aspartic acid (NMDA) receptors (see Chapter 8). Changes similar to those involved in long-term potentiation then occur within dorsal horn cells. However, there is an important difference. Whereas long-term potentiation occurs locally in the synapse receiving strong input, central sensitization affects all synapses in the postsynaptic cell. The result of these universal changes is an enhanced response to all afferent input (Fig. 18-9). This is the mechanism by which central sensitization results in an augmented response to both innocuous and noxious inputs. After central sensitization, inputs that were ineffective at eliciting a response in a dorsal horn cell become effective. Since these subthreshold inputs arise from regions at the margins of the receptive field, the receptive fields of dorsal horn neurons are expanded after central sensitization.

REFERRED PAIN DEPENDS ON THE CONVERGENCE OF INPUT FROM SUPERFICIAL AND DEEP INPUTS ONTO CENTRAL NEURONS

Just as we learn to interpret points of light and dark as visual images and auditory tones as meaningful communication, we learn to interpret input from somatosensory pathways as stimulation of our body. A baby learns to associate one particular neural pattern with touch of the right thumb pad and a different neural pattern with heat on the lip and so on. Such associations can be learned for superficial structures because there are data to interpret. Falling and scraping a knee produces activity in visual, auditory, and multiple somatosensory pathways. And the inputs from multiple systems vary systematically according to the site of a stimulus. Using such information, the cerebral cortex learns to correctly assign activity patterns to stimuli of a given nature at a given location. In essence, we learn to *project* activation within somatosensory areas of cerebral cortex as touch or pressure, heat, or cold, or pricking, and so on.

In contrast to superficial stimulation, stimulation of deep structures produces only a somatosensory feeling with no other sensory information to anchor that feeling. As a result, we cannot learn the characteristics or the location of stimuli arising from deep structures. Moreover, afferents from deep structures and afferents from cutaneous structures converge onto the same dorsal horn cells (Fig. 18-10).

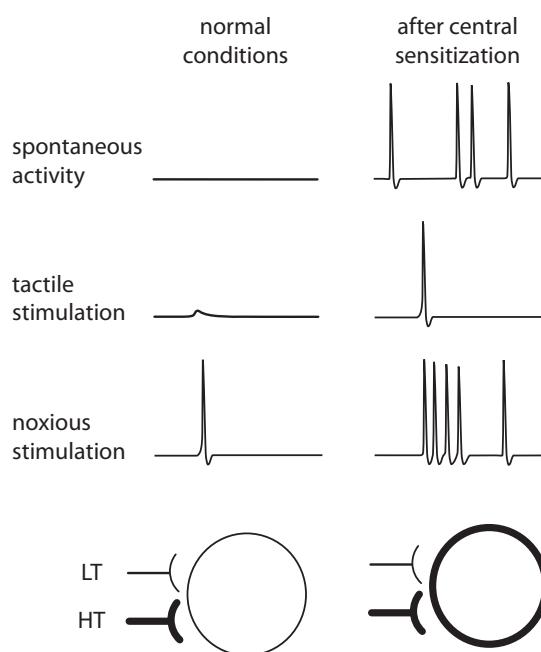
CHRONIC PAIN OR INFLAMMATION PRODUCES TISSUE DEGRADATION.

Arthritis is a heterogeneous group of conditions that all involve joint damage usually accompanied by pain. Arthritic conditions are prevalent, affecting more than a fifth of American adults. Arthritis is more prevalent among women during their reproductive years than among men. This sexual difference appears to depend at least in part upon gonadal hormonal differences as rheumatoid arthritis is ameliorated during pregnancy and in women taking contraceptive pills.

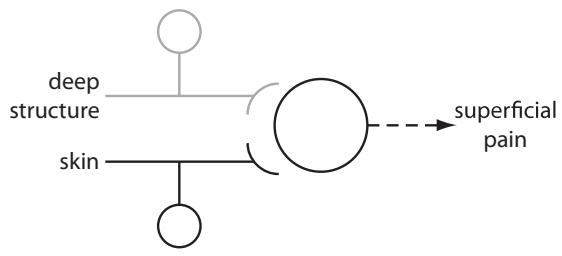
In arthritis, inflammatory and algesic compounds transform silent nociceptors into a responsive state. Whereas before the transformation, silent nociceptors can only be activated by electrical stimulation, afterward, they respond to simple joint flexion and extension. This stunning experimental finding explains the severe pain suffered by individuals with arthritis while making even the simplest movements.

The mechanisms by which chronic arthritis degrades tissue, and the neuronal contribution to this degradation, are under active investigation. At least in some cases, tissue destruction and exaggerated pain may stem from a common pathway. For example, serine proteases are elevated in inflamed tissue and thus comprise part of the inflammatory soup. By breaking down proteins within the knee joint, proteases directly contribute to the degradation of the inflamed tissue. Proteases also lead to the activation of metabotropic **protease-activated receptors**, or **PARs**, which are found on nociceptors. Nociceptors exposed to PAR agonists fire action potentials spontaneously and also respond to innocuous stimulation. Pain and tissue destruction through common inflammatory mechanisms are aggravated by an increase in synovial volume and by changes in joint usage and mechanics due to pain.

Figure 18-9. Under normal conditions, high-threshold nociceptive dorsal horn neurons are not spontaneously active and only fire an action potential in response to noxious stimulation. Low-threshold tactile stimulation evokes an excitatory postsynaptic potential (EPSP) but not an action potential. After central sensitization, spontaneous activity and the responses to innocuous or low-threshold (LT) and nociceptive or high-threshold (HT) inputs are greater.



A. normal conditions



B. during conditions of deep pain

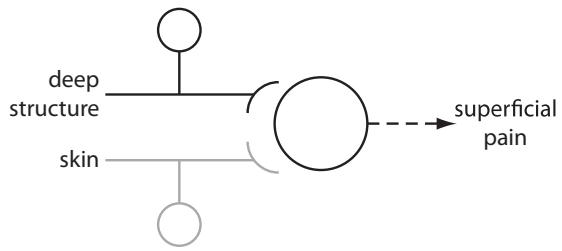


Figure 18-10. Referred pain arises from a convergence of deep and superficial input onto single dorsal horn cells. Under normal conditions (A), the superficial input is sometimes active, but the deep input is never active. Therefore, higher structures learn to interpret activity in the dorsal horn cell as arising from the superficial structure. Activity in deep nociceptors (B), when it occurs, excites a dorsal horn cell whose activity is associated with superficial pain. As a consequence, noxious stimulation of a deep structure is interpreted as arising from superficial structures.

For example, a single spinothalamic tract cell in the thoracic spinal cord may receive input from a visceral afferent that innervates the stomach and from a cutaneous afferent innervating the skin of the upper abdomen. Activity in that spinothalamic tract cell is interpreted as stimulation of the abdominal surface, *not* of the stomach. Convergent excitation from visceral and superficial afferents of sensory neurons in the dorsal horn and spinal trigeminal nucleus produces a *referral* of deep pain to the body surface. This is the basis for **referred pain**.

Deep afferents converge with cutaneous afferents onto dorsal horn cells that receive input from nociceptors but not onto dorsal horn cells that receive input exclusively from innocuous mechanoreceptors. As a result, we experience deep stimulation as *pain* rather than as vibration or light touch for example. Nonetheless, the complement of somatosensory activity elicited by deep stimuli differs from the complement of somatosensory activity activated by a normal cutaneous stimulus. For example, no innocuous mechanoreceptive input arises from regions at the margin of the central skin region. Because the sensation elicited is unlike anything caused by a normal cutaneous stimulus, we are often aware that the stimulus arises from “inside.”

THE BRIDGE TO PERSISTENT PAIN IS PAVED BY PERIPHERAL AND CENTRAL CHANGES

Persistent pain is not simply acute pain of long duration. Persistent pain has different characteristics than acute pain because important properties of the nociceptors, peripheral tissue, and central pain pathways are significantly altered. When acute pain turns into a chronic state, the nervous system is altered, often permanently, so that even if any peripheral damage present were rectified, the pain would continue. In other words, persistent pain occurs independently of any stimulus; this is the meaning of the term *neuropathic*. A particularly poignant example of neuropathic pain is **phantom limb pain**, in which the perceived source of the painful sensation does not even exist. As phantom limb pain exemplifies, nociceptive transmission is uncoupled from any physical stimulus in conditions of neuropathic pain.

Neuropathic pain usually involves three positive signs—**allodynia**, **hyperalgesia**, and **spontaneous pain**. One of the most disturbing symptoms experienced by patients with chronic pain is allodynia, the perception of pain in response to innocuous stimulation. For example, a patient with neuropathy may feel the touch of clothing as exquisitely painful. A person with a headache may experience the pulsation of a blood vessel as a jackhammer pounding on the skull. As one can imagine, allodynia causes great distress and significantly decreases quality of life. Further, **spontaneous pain** often occurs in neuropathic pain conditions. In hyperalgesia, pain sensations are enhanced so that, for example, a stimulus that ordinarily produces pain rated as 3 on a scale of 1 to 10 now produces a pain rated as 9. Spontaneous pain can have a variety of qualities from lancinating and electrifying to throbbing and aching. It is unclear

whether spontaneous pain is indeed spontaneous or is triggered by stimuli, such as intestinal peristalsis or body temperature that normally do not elicit any perception.

Three types of injuries are the most common triggers of the transition to neuropathic pain:

- *Inflammation*: Injuries caused by trauma, infection, or disease are often accompanied by tissue inflammation.
- *Nerve injury*: Damage or disease of the peripheral nerve alters the properties of the dorsal root ganglion neurons whose axons are injured.
- *Deafferentation*: Interruption of sensory pathways, either peripherally or centrally, causes changes in cells previously targeted by the damaged and now absent input (see Box 18-12).

Inflammation, nerve injury, and deafferentation produce some changes in common, whereas other changes occur more under certain circumstances than others. For example, changes in the chemical environment at the site of injury are critical to persistent inflammatory pain but contribute little or not at all to deafferentation pain. The changes involved in initiating persistent pain operate at three essential levels:

- The chemical environment of peripheral tissue
- The nociceptor
- Central pathways

Box 18-12

POSTHERPETIC NEURALGIA IS A NEUROPATHIC PAIN THAT RESULTS FROM THE LOSS OF SENSORY AFFERENTS.

Recall from Box 9-6 that herpes zoster, commonly called **shingles**, is an exquisitely painful rash caused by an awakening of latent **varicella zoster virus**, the causative agent for chicken pox, present in sensory neurons of the dorsal root or trigeminal ganglia. The pain of herpes zoster represents a good example of acute somatic pain. Treatment with antiviral drugs can shorten the duration of a herpes zoster outbreak and analgesics may relieve the pain experienced.

Unfortunately, the story does not always end once an outbreak of herpes zoster resolves. In up to a quarter of patients, a chronic pain condition called **postherpetic neuralgia** develops. Postherpetic neuralgia, often abbreviated as PHN, is a potentially devastating, life-altering disease. Common risk factors for the development of postherpetic neuralgia

are an older age at onset of herpes zoster, severity of the zoster rash, and pain severity at the time of the initial zoster infection. Postherpetic neuralgia is characterized by allodynia and spontaneous pain that can be either deep and aching or sharp and lancinating, or both. In cases where postherpetic pain is accompanied by local anesthesia, the implication is that infected dorsal root ganglion cells have died, setting up a deafferentation-type pain classically termed **anesthesia dolorosa**.

A recently developed vaccine reduces the incidence of herpes zoster and postherpetic neuralgia by more than 55%. Although expensive, this vaccine is now being provided to the at-risk populations of immunocompromised and elderly individuals.

Changes at each of these levels work together to produce the symptoms of persistent pain. Chronic pain is, by definition, a positive sign. If, for example deafferentation or nerve injury produced a negative sign, then either anesthesia, an absence of feeling, or analgesia, an absence of pain, would result. Although anesthesia is often present, individuals with somatosensory dysfunction are far more bothered by the experience of *paresthesias*, abnormal sensations that, when unpleasant, are termed *dysesthesia*s. Examples include sensations of numbness, pins and needles, or impalement by a hot poker.

Certain proteins are particularly important to nociceptor function and appear to have less import to the normal function of other types of afferents. Among these proteins are several sodium channel isoforms that are present exclusively in nociceptors or are found at particularly high levels in nociceptors (see Box 18-13). These sodium channel isoforms convey two important properties to nociceptors:

- *Threshold for activation*: The sodium channels present in nociceptors open at depolarized potentials. Therefore, the threshold for eliciting an action potential is more depolarized than in other cells.
- *Duration of action potential generation*: Once activated, nociceptors fire only one or a few action potentials.

The importance of the elevated threshold and limited firing pattern to nociceptors is revealed when these firing characteristics are altered by injury. During conditions of persistent pain such as inflammation, nerve injury, or a burn injury, nociceptors change. The threshold for activation is lowered and inactivation occurs more slowly. Therefore, in persistent pain conditions, less intense stimuli, often in the innocuous range, activate nociceptors and elicit bursts of action potentials rather than single spikes. Furthermore, the number of sodium channels is elevated. All of these changes are critical to the *paroxysmal*, meaning electric and shooting, pain experienced by some individuals in chronic pain.

Box 18-13

INDIVIDUALS WITH MUTATIONS IN SODIUM CHANNEL SUBUNITS ARE INSENSITIVE TO PAIN.

Mutations in $\text{Na}_v1.7$, the sodium channel isoform important in action potential generation in nociceptors, cause a congenital insensitivity to pain. Individuals with nonsense mutations in $\text{Na}_v1.7$ feel no pain and thus present in a manner similar to that of children with hereditary autonomic and sensory neuropathy or HSAN (see Box 9-2). However, these children appear to have fewer symptoms of sympathetic dysfunction, such as anhidrosis.

ULTIMATELY THE BRAIN CONTROLS WHAT WE FEEL THROUGH SOMATOSENSORY PATHWAYS

An intriguing aspect of somatosensory perception is its lability. There are two major modulatory systems involving descending projections:

- During movements, anticipated sensory inputs are suppressed. Every self-generated movement creates changes that are sensed by cutaneous afferents. Yet, as long as the changes that occur are those that are expected to occur, central transmission of the sensory inputs is suppressed. This indeed makes it impossible to tickle oneself. The suppression is accomplished by projections from somatosensory cortex to the dorsal column nuclei and the dorsal horn.

Box 18-14

THE ANALGESIC EFFECTIVENESS OF OPIOIDS IS MEDIATED BY ENDOGENOUS PAIN MODULATORY CIRCUITS.

Opioids, such as fentanyl or morphine, are the prototypical analgesic in clinical use today. The reason that opioids are so effective at alleviating pain is that opioid receptors are present throughout nociceptive transmission circuits. The distribution of opioid receptors throughout pain pathways allows opioids to act at multiple levels. Actions of μ -opioid receptor agonists within the spinal cord are effective in blocking the transmission of nociceptive transmission. This is the basis for epidural administration of opioids. Recall from Chapter 14 that within the spinal cord, there is a space between the bone and the dura. Epidural injections are given into this space. Drugs that cross the blood–brain barrier reach the spinal cord from the epidural space in relatively high concentrations. Epidurally administered opioids are used to relieve acute pain during childbirth, surgery, and postsurgical recovery and for the treatment of chronic pain, often in terminally ill patients with intractable pain.

The other important sites where opioids act to modulate pain transmission are within the brainstem. Neurons in the periaqueductal gray (see Chapter 12) and a midline nucleus in the medulla,

the **raphe magnus**, respond to opioids by suppressing nociceptive transmission within the spinal cord and the spinal trigeminal nucleus. The suppression of nociceptive transmission initiated by brainstem neurons is termed **descending pain modulation** as it is carried by neurons in the raphe magnus that descend to the spinal cord. The relevance to clinical practice of descending pain modulation is two-fold. First, the analgesic effects of opioid actions in the brainstem and spinal cord are synergistic. Thus, opioids administered systemically (orally or by injection) produce a more powerful analgesia than when administered only epidurally or only in the brainstem. The second unfortunate point of relevance is that the side effects of systemic opioids are the inevitable consequence of the modulatory effects exerted by the periaqueductal gray and raphe magnus on many physiological processes beyond nociceptive transmission. At present, it is not clear how to fully engage the analgesic power of opioids without also eliciting changes in thermoregulation, cardiorespiratory function, bladder control, and the like.

Box 18-15

TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION IS A SAFE, NONINVASIVE TREATMENT THAT ALLEVIATES PAIN IN SOME PATIENTS.

As $A\beta$ afferents enter the spinal cord and course rostrally within the ipsilateral dorsal column, they give off collaterals that enter the dorsal horn. These collaterals are the source of tactile input to dorsal horn cells. Activity in $A\beta$ afferents has an inhibitory effect on nociceptive transmission. This circuitry may explain why devices that electrically stimulate nerves transcutaneously are effective in alleviating pain in many patients. **Transcutaneous electrical**

nerve stimulators or **TENS units** are noninvasive and entirely safe. Since $A\beta$ afferents have a lower electrical threshold than do other nerve fibers, it is straightforward to adjust the stimulation intensity to a level that only stimulates $A\beta$ afferents. Nowadays, TENS units are compact and can easily be worn over extended periods of time. As TENS units provide great relief to many patients and carry few risks, they are often worth trying if the funds are available.

The suppression of anticipated sensory inputs allows us to register surprises or unexpected events and to ignore mundane and uninformative inputs.

- Brainstem regions including the periaqueductal gray can bidirectionally modulate nociceptive transmission within the dorsal horn. Activity in descending pain modulatory pathways can on one hand, enhance pain reactions, and on the other hand, suppress nociceptive transmission. This modulatory pathway plays important roles in both opioid analgesia (see Box 18-14) and neuropathic pain.

In addition to descending modulatory systems, local spinal circuitry supports modulation of the interaction between tactile and nociceptive pathways. One example of this is the inhibition of nociceptive transmission by activity in local A β mechano-receptors. This type of interaction may be the reason that shaking an injured finger or blowing on a burn alleviates the pain of the injury. The inhibition of nociceptive transmission by A β activity is also the basis for the most efficacious, nonpharmacological therapeutic treatment for pain, **transcutaneous electrical nerve stimulation** or **TENS** (see Box 18-15).



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CHAPTER 19

THE VESTIBULAR SENSE: BALANCE AND EQUILIBRIUM

HEAD POSITION AND MOTION ARE DETECTED BY THE VESTIBULAR SYSTEM

Airplanes, ships, and cars have a set of gyroscopes that detect orientation with respect to gravity. We have an even more sophisticated set of orientation and position sensors within the vestibular apparatus inside our head. Using the vestibular system, we can tell when an elevator starts moving even though there are no visual cues. If the elevator is moving at a steady speed, it is no longer possible to detect movement. Similarly, an ornament hanging from the rear view mirror of a car only swings backward and forward during accelerations and decelerations. When the car is in constant motion, the ornament is steady *with respect to the car* even as the ornament careens forward, along with the car, at so many miles or kilometers per hour. The principle that objects maintain a constant velocity unless a force acts upon them is referred to as *inertia* and is also known as Newton's first law.

The vestibular system uses the principle of inertia to provide a sense of head position, orientation, and motion. Just as an ornament hangs from the car mirror, there are two weights, called the *otoconial masses*, which are acted upon by gravity and by linear head accelerations. Movement of the otoconial masses provides the sensory information from which we derive a sense of head position. We are also sensitive to rotational movements of the head. Any head movement always involves an acceleration from an initial position and a deceleration at the end of the movement. The acceleration of the head during rotational movements leads to fluid movement within the *semicircular canals*. Fluid movement in the semicircular canals, and the positions of the otoconial masses are detected by vestibular hair cells.

Recall from physics that the integral of acceleration is velocity. Vestibular hair cells make this calculation, so that head acceleration elicits a response that is proportional to head velocity. When velocity is not changing, we do not detect any

Box 19-1

GAZE DEPENDS ON BOTH HEAD AND EYE POSITION.

The direction of our gaze depends on the position of our head, as well as the direction of fixation. Small gaze shifts of up to about 20 degrees, such as those used to read this book, are accomplished using eye movements primarily with little or no head movement. Even when making large gaze shifts, movements of the eyes account for more of the gaze shift than does movement of the head (see Chapter 26).

head movement. This allows us to walk around without constantly *sensing* the downward force of gravity.

Vestibular afferents inform the central nervous system about the direction and speed of head movement. The brain uses this information in a variety of reflexes that function to stabilize gaze (see Box 19-1), to stabilize the head with respect to the body, and to stabilize the trunk and limbs with respect to gravity. The close link between the vestibular sense, vision, and the motor system serve to keep the body in balance or equilibrium. The influence of the vestibular system on motor control is so automatic, and necessarily so, that we take balance, equilibrium, and a steady visual image entirely for granted.

The vestibular system is a phylogenetically ancient system. Virtually all vertebrates have a vestibular apparatus, and most animals have gravity sensors. Remarkably, even plants have a mechanism to detect the direction of gravitational forces, which is used to direct root growth downward, toward the center of the Earth, rather than perpendicular to the ground. The ubiquity of gravitational sensory systems in both the plant and animal kingdoms speaks to the fundamental importance of adjusting growth and position to Earth's gravity.

Vestibular information can be used for conscious recognition of the position and motion of the head. Under normal conditions, we are not conscious of the fact that we are upright in the same sense that we are conscious that the sky is blue, the birds are singing, or a cool breeze is in the air. It appears that our perception of equilibrium *adapts* extraordinarily quickly, vanishing from our consciousness even more rapidly than does awareness of the touch of our clothes. We also do not think anything of the steady visual image that we see from moment to moment. Yet, under pathological conditions, including alcohol intoxication, vestibular dysfunction creates disturbing perceptions of *oscillopsia*, *vertigo*, and *disequilibrium* that, when present, dominate our conscious experience and grab our attention.

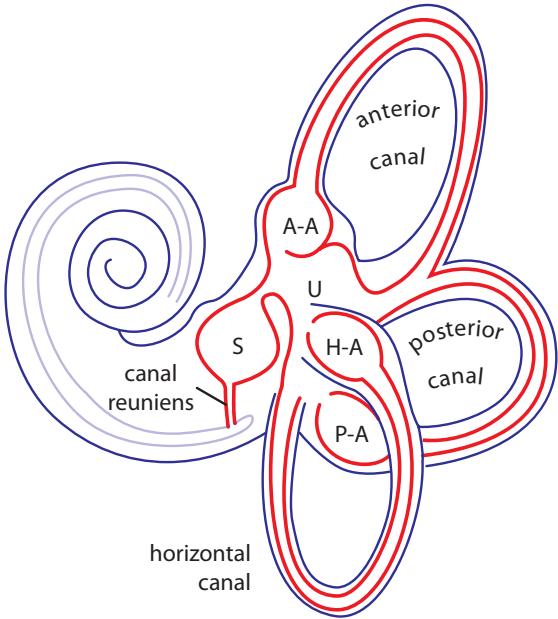
Motor and autonomic consequences of vestibular dysfunction indirectly lead to abnormal perceptual experiences. For example, *disequilibrium*, which refers to an impaired postural stability that commonly accompanies vestibular dysfunction, results in a feeling of unsteadiness. *Nystagmus*, an oscillatory eye movement (see much more in Chapter 26) that occurs normally under certain conditions, is at other times a pathological symptom of vestibular dysfunction and produces *oscillopsia* or *diplopia*. Vestibular dysfunction often commonly produces autonomic symptoms such as nausea. Autonomic symptoms can occur alone, as in some cases of *motion sickness*, or can be accompanied by an abnormal perception such as *vertigo*.

In this chapter we consider:

- The peripheral vestibular apparatus
- Vestibular afferents
- Central pathways involved in the perception of equilibrium

We start by returning to the inner ear, the subject of much of Chapter 17, where both the cochlea and the vestibular end organs are located (Fig. 19-1).

Figure 19-1. The membranous labyrinth, outlined in red, sits within the bony labyrinth (blue). The three semicircular canals form the most posterior portion of the inner ear. All three semicircular canals open up into the utriculus (U). The sensory epithelium for each canal is contained in a swelling called an ampulla. The ampullae of the anterior (A-A), posterior (P-A), and horizontal (H-A) semicircular canals are labeled. Anterior to the utriculus is the sacculus (S). The entire membranous labyrinth is bathed in endolymph, which is formed within the cochlea. Endolymph reaches the labyrinth through the narrow canal reunions.



THE VESTIBULAR LABYRINTH IS PART OF THE INNER EAR

The vestibular labyrinth uses the same general mechanisms to respond to head motion as the cochlea uses to respond to airborne sounds. In both structures, the transducing sensory cell is a hair cell, and afferent neurons send axons to the central nervous system through the same cranial nerve, the vestibulocochlear nerve. Hair cells in the vestibular labyrinth and cochlea are bathed in the same fluid, endolymph. Indeed endolymph is made by the stria vascularis within the cochlea and then flows through the **canal reunions** to bathe the vestibular end organs as well (Fig. 19-1). In both inner ear structures, *the ultimate stimulus sensed by hair cells is mechanical displacement of the hair cell stereocilia*. The principal difference between the two structures lies in how the adequate stimulus for each—airborne sound in the case of the cochlea and head motion in the case of the vestibular labyrinth—are transformed into mechanical displacement of hair cell stereocilia.

TWO TYPES OF VESTIBULAR END ORGANS ARE STIMULATED BY TWO TYPES OF HEAD ACCELERATION

The vestibular labyrinth can be functionally divided into two parts—the *semicircular canals* and the *otoconial organs*. **Angular acceleration** of the head stimulates hair cells in the semicircular canals, whereas **linear accelerating forces**, including *gravity*, stimulate hair cells within the otoconial organs. Angular head acceleration is the acceleration produced by rotational motion of the

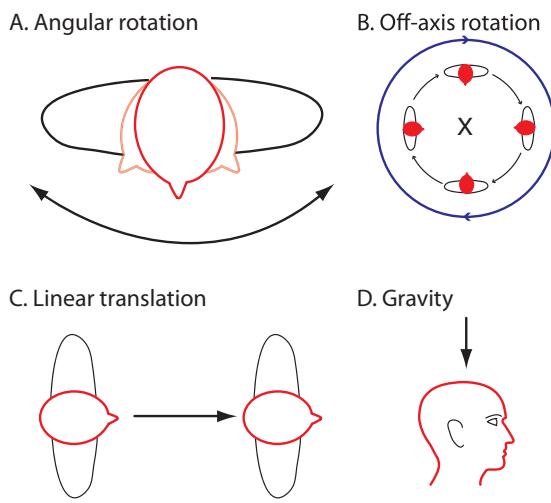


Figure 19-2. A: An example of an angular rotation in the horizontal or yaw plane is illustrated. The center of the angular rotation shown in A is the midpoint of the head. B: Angular rotation can also occur off-axis, as when a person rides a merry-go-round. C: Linear motion, or translation, follows a simple linear path. D: Gravity is a constant acceleration of about 10 m/s^2 .

head (Fig. 19-2A), such as occurs on a merry-go-round or when shaking the head to indicate “no.” Note that the central axis of rotation when shaking your head is the center of the head. In contrast, when sitting on the merry-go-round, the center of rotation is the center of the merry-go-round; this is termed **off-axis** rotation (Fig. 19-2B). The semicircular canals respond to both on- and off-axis rotational movements of the head.

Linear head acceleration is acceleration of the head along any linear path of motion. Running forward, jumping up, falling down, and stepping sidewise all involve linear motion (Fig. 19-2C). Gravity, an acceleration of roughly 10 m/s^2 , operates upon us even when we stand still or lie down (Fig. 19-2D). Because of gravity, static head tilt, which is simply the position of the head with respect to gravity, stimulates responses in the otoconial organs.

Impairment of the otoconial organs typically produces disequilibrium whereas impairment of semicircular canal function results in vertigo (see Box 19-2). Beyond these perceptual symptoms, vestibular impairment also produces disordered eye movements such as nystagmus that result in visual disturbances such as diplopia and oscillopsia.

THERE IS A SPECIALIZED SENSORY EPITHELIUM IN EACH VESTIBULAR END ORGAN

The **utriculus** and **saccus** occupy a vestibule located posterior to the cochlea and anterior to the three canals. The utriculus is located more caudally and opens into the semicircular canals (Fig. 19-1). The utriculus and saccus each contain a patch of hair cells called the **macula**. Stereocilia of the macular hair cells are embedded in a gelatinous structure called the **otoconial mass** that contains about 200,000 **otoconia** (Greek for *ear dust*). Each otoconium (the singular form of otoconia) consists of a matrix of glycoproteins and crystals of calcium carbonate (see Box 19-3). Since the density of the otoconial mass is higher than that of endolymph, the otoconial mass serves as a weight, or load, and falls in response to gravity.

There are three semicircular canals on each side. The canals are fluid-filled **tori** (**torus** is the singular form), meaning shapes that resemble inner tubes. The three canals, oriented orthogonal to one another in three planes of space, are:

- The **anterior**, or **superior**, semicircular canal
- The **posterior**, or **inferior**, semicircular canal
- The **horizontal**, or **lateral**, semicircular canal

DISEQUILIBRIUM, VERTIGO, AND DIZZINESS ARE THE MOST COMMON PATHOLOGICAL VESTIBULAR PERCEPTIONS.

Common perceptual consequences of vestibular dysfunction are disequilibrium and vertigo. Disequilibrium is a compromise of the sense of balance, often accompanied by a perception of spatial disorientation. Damage to the otoconial organs, for example by loss of the saccus on one side to toxic damage, is one cause of disequilibrium. An individual with disequilibrium does not feel in balance even when he or she is. In addition, disequilibrium results in postural instability and unfortunately in mishaps including injurious falls. Fear of falling and the uncertainty of feeling unbalanced leads some individuals with disequilibrium to retreat from the world and social interactions. The incidence of disequilibrium increases greatly with age.

Vertigo refers to a perception of spinning, either that the world is moving around a stationary individual or that the self is spinning within a stationary environment. Vertigo results from canal dysfunction. Dizziness refers to an uncomfortable sensation of lightheadedness or the feeling that one is about to faint. Dizziness is most often caused by problems outside of the vestibular system, particularly problems with the cardiovascular system such as hypovolemia. Simply getting up too quickly can sometimes produce a completely benign lightheadedness. Thus, dizziness is by no means an automatic sign of vestibular dysfunction. Despite the distinct definitions of dizziness and vertigo, lay people often use these terms, particularly dizziness, to refer to a wide variety of uncomfortable sensations. It is important therefore to ask an individual reporting dizziness or vertigo to describe their sensations. Recurring

episodes of true vertigo typically indicate a problem with the vestibular system.

Oscillopsia and diplopia are visual disturbances that are the indirect result of vestibular impairment. The intermediary between vestibular damage and these visual problems is abnormal eye movements, particularly nystagmus. Nystagmus refers to an eye movement in which the eyes repeatedly oscillate back and forth. In the most common type of nystagmus, the eyes drift in one direction, reach the limit of the orbit, quickly return to the neutral position, drift again, and so on. There are benign forms of nystagmus. In fact, *optokinetic nystagmus*, such as occurs after twirling around (see Chapter 10) or when looking at a picket fence (or any repeating pattern) while traveling in a moving vehicle, is a sign of vestibular health.

Nystagmus also occurs in a variety of central and peripheral vestibular pathologies. The perceptual result of nystagmus is a disturbance in the continuity of the visual image. When nystagmus is present in one eye, diplopia, or double vision, results (see Chapter 26). If nystagmus is present in both eyes, and both eyes move together, oscillopsia occurs. Oscillopsia is very disturbing. In an individual with oscillopsia, the world moves continuously, with every body and head movement or when the head is stationary. This is akin to watching the world through a hand-held video camera. Movies that intentionally use this device for effect make many movie-goers feel nauseated. In oscillopsia, the moving visual image persists far longer than the 90–120 minutes of a film. The effect can be not only disturbing but also debilitating.

Each semicircular canal begins and ends in the utricle. At one end of each semicircular canal is a swelling called the **ampulla** (Fig. 19-1). Within the ampulla, there is a ridge of sensory epithelium that traverses the canal (Fig. 19-3). This sensory epithelium is the **crista ampullaris**, or simply the **crista**, where the hair cells are situated. The stereocilia of hair cells in the crista extend upward into a gelatinous structure, the **cupula**, which stretches across the lumen of the canal.

THE MAMMALIAN OTOCIONAL MASS IS DISTINCT STRUCTURALLY AND DEVELOPMENTALLY FROM THE OTOLITH OF FINNED FISH.

An otoconial mass contains about 200,000 tiny weights called otoconia. Each otoconium consists of calcium carbonate within a matrix of glycosylated proteins called **otoconins**. The otoconia amass together into an otoconial mass, which is a collection of otoconia held together by fibrils and goo. Otoconins are only secreted during fetal development, and the mature otoconial masses form at that time.

The otoconial mass found in mammals differs substantially from the otolith found in fish. The otolith of finned fish is a *unitary mass* of calcium carbonate within a proteinaceous matrix that continues to grow throughout the lifetime of a fish. The otoconial mass and otolith both serve as a load or weight that enables the facile detection of the direction of the gravitational force. Nonetheless, the differences between otoconial masses and otoliths are substantial and therefore, the term *otoconial mass* is used here in place of the ubiquitously used misnomer otolith.

Unfortunately, the supply of otoconia formed during development does not always last for a human lifetime as the otoconial masses degenerate with age. Decalcification of the otoconia and loss of

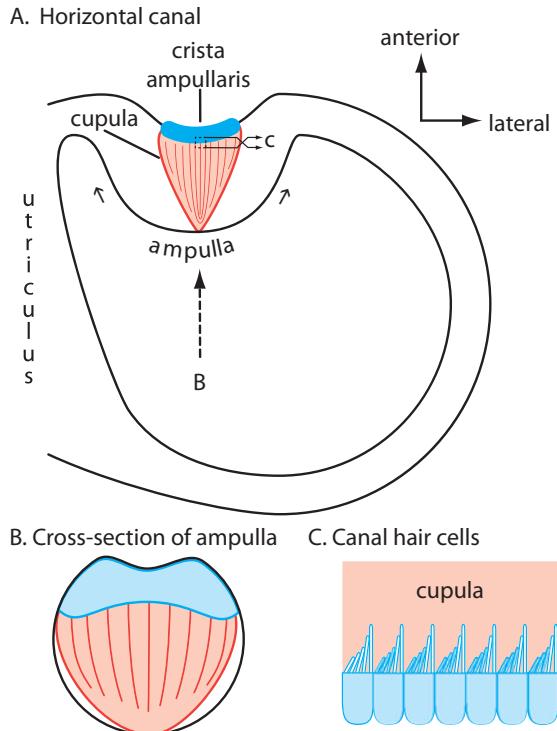
fibrils leads to a progressive degeneration of the otoconial masses that starts by the sixth decade. The degeneration first appears as pits in the otoconial masses. With time, the pits expand until the otoconial masses are broken into small pieces, which break loose and eventually float off. As the degeneration of otoconia occurs preferentially in the saccus, the saccus eventually lacks otoconia altogether in affected individuals.

If the loss of otoconia from the otoconial masses is balanced between the left and right ears, there may be little effect on equilibrium. However, a total or near-total loss of the otoconial masses would certainly adversely affect balance and contribute to disequilibrium. Because of the finite supply of otoconia, degeneration of the otoconial masses is a progressive problem. As discussed in Box 19-2, disequilibrium is a debilitating state that can lead both to falls and to social isolation born of the fear of falling. It may be that impairment in balance secondary to otoconial mass degeneration is as inevitable or likely as other age-related changes, such as presbyopia and presbyacusis. This understudied topic presents a challenge for future physicians.

VESTIBULAR HAIR CELLS RESPOND TO MOVEMENT OF THE STEREOCILIA TOWARD OR AWAY FROM THE KINOCILIUM

Vestibular hair cells function very similarly to cochlear hair cells (see Box 19-4). Movement of the stereocilia toward the **kinocilium**, the tallest stereocilium, is the preferred direction (Fig. 19-4). In response to movement in the preferred direction, the hair cells depolarize. When the stereocilia are bent

Figure 19-3. A: The horizontal canal opens into the utricle at both its anterior and posterior ends. The ampulla of the horizontal canal is located anteriorly. Within the ampulla, the sensory epithelium, termed a crista ampullaris (blue), is located on top of the ridge of the crista. The stereocilia of the hair cells within the crista are embedded in a gelatinous structure called a cupula. B: A cross-section through the ampulla at the point labeled B in A is shown. The cupula covers the entire crista and stretches across the lumen of the canal. C: Hair cell stereocilia are embedded within the cupula.



away from the kinocilium, the nonpreferred direction, hair cells hyperpolarize. Recall from Chapter 17 that hair cell transduction depends on tip links that connect shorter stereocilia to longer stereocilia. When the stereocilia are displaced toward the kinocilium, the tip links pull on the mechanoelectrical transduction channel, resulting in a higher probability of channel opening. Opening the mechanoelectrical transduction channel, a cationic channel, results in cell depolarization. Conversely, when the stereocilia are displaced away from the kinocilium, there is a lower probability of channel opening, and the hair cell hyperpolarizes. Bending the stereocilia orthogonal to the preferred-to-nonpreferred axis has no effect on the tip links and therefore does not elicit a hair cell response.

Within each semicircular canal crista, all hair cells are oriented in the same direction (Fig. 19-5A). Therefore, displacement of the cupula in one direction depolarizes canal hair cells and displacement in the other direction hyperpolarizes hair cells (Fig. 19-5). The hair cells in the saccular macula are oriented vertically, responding to a vertical displacement of the stereocilia with either a depolarization or a hyperpolarization (Fig. 19-6A). The orientations of hair cells in the utricular macula are radially organized to cover all horizontal directions. Consequently, displacement of the utricular stereocilia in any horizontal direction depolarizes a population of utricular hair cells, hyperpolarizes another population (Fig. 19-6C), and has no effect on utricular hair cells with an orthogonal orientation.

MANY COCHLEAR DISORDERS INVOLVE VESTIBULAR DYSFUNCTION AS WELL AND VICE VERSA.

The cochlea and vestibular apparatus share common developmental and physiological processes. As a result, many congenital forms of deafness also involve at least some degree of vestibular impairment. There are of course exceptions, such as deafness caused by mutations in *prestin*, the molecular motor in outer hair cells, which occurs without any vestibular dysfunction. The susceptibility of cochlear hair cells to ototoxic drugs (see Box 17-12) is also shared by vestibular hair cells although most drugs preferentially harm one type of hair cell over the other. Streptomycin and gentamicin are examples of antibiotics that affect vestibular hair cells more than cochlear hair cells.

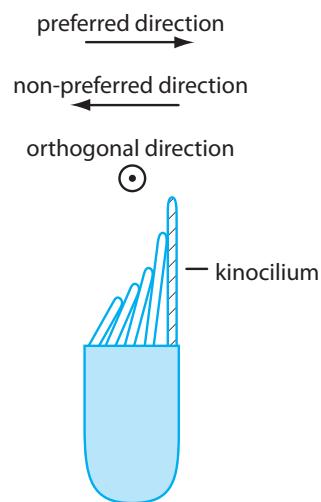
Ménière's disease is a disabling disease that involves recurring episodes of vertigo, hearing loss, and tinnitus, with a sensation of fullness in the ear. Typically, the most distressing and disabling aspect of Ménière's disease is the vertigo that is experienced. Nausea, disequilibrium, and rarely spontaneous falls or drop attacks can accompany the episodes of vertigo. The drop attacks are thought to reflect an impairment of the saccular response to gravitational force that is so important in keeping us upright.

Associated with the incidence of Ménière's disease is an increase in endolymphatic pressure, termed **endolymphatic hydrops**, which can result

from either overproduction or insufficient absorption of endolymph. There is evidence for endolymphatic hydrops in patients with Ménière's disease but also in healthy individuals. Treatment with diet restrictions and steroids designed to reduce endolymphatic pressure ameliorate the vestibular symptoms of Ménière disease's in many patients. Unfortunately, even after such treatment, disabling vertigo continues to afflict about 10% of patients with Ménière's disease. Many of these patients elect to undergo either a surgical ablation of the vestibular apparatus or injections of the ototoxic gentamicin into the affected labyrinth in order to rid themselves of the vertigo. The willingness of patients to undergo these procedures, which cause permanent vestibular impairment, speaks to the extreme distress of the vertiginous episodes experienced by patients with Ménière's disease.

An inflammation of the inner ear, termed **labyrinthitis**, or of the vestibular branch of the vestibulocochlear nerve, **vestibular neuritis** or **neuronitis**, causes a rapid onset of symptoms such as vertigo, disequilibrium, and nausea. As labyrinthitis affects the entire inner ear, some hearing loss and tinnitus also occur. Labyrinthitis and vestibular neuritis are thought to be caused by a viral infection in most cases. In both disorders, symptoms typically subside in days to weeks.

Figure 19-4. Hair cell stereocilia are arranged from shortest to tallest. The tallest stereocilia is called a kinocilium. Deflection of the stereocilia toward the kinocilium is the preferred direction of stimulation and results in hair cell depolarization. Deflection of the stereocilia away from the kinocilium is the nonpreferred direction of stimulation and results in hair cell hyperpolarization. Hair cells do not respond to deflection of the stereocilia in the orthogonal direction (into or out of the page).



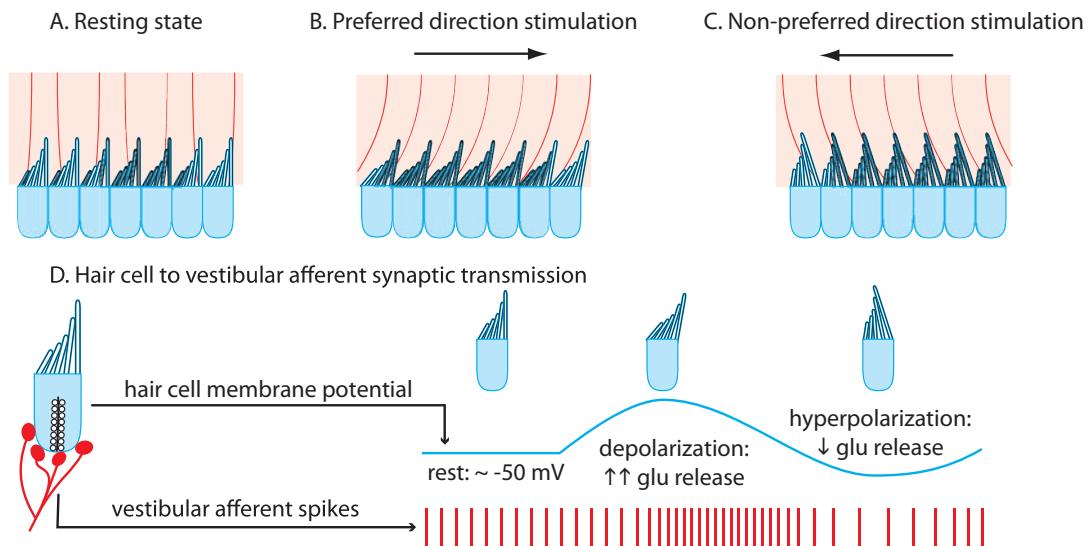
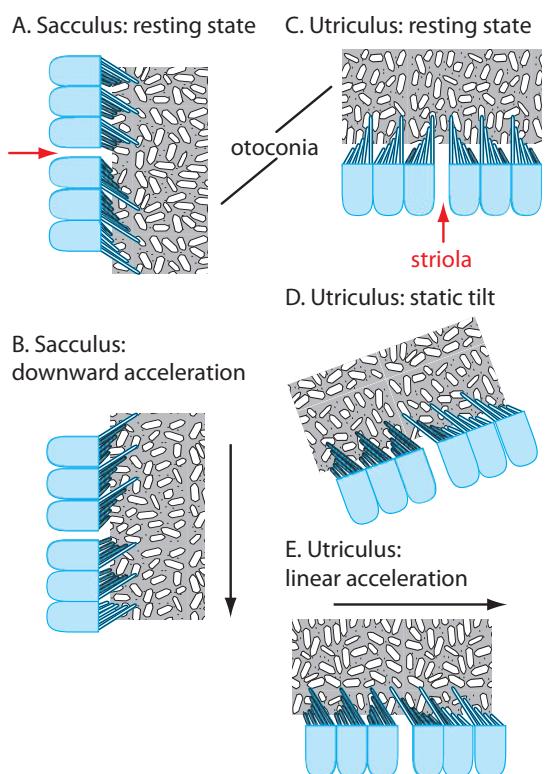


Figure 19-5. **A:** All canal hair cells have the same orientation. In the resting state, hair cell stereocilia are in a neutral position. **B:** Endolymph flow in the preferred direction deflects the cupula, which in turn deflects the stereocilia toward the kinocilium. **C:** Endolymph flow in the nonpreferred direction deflects the cupula, which in turn deflects the stereocilia away from the kinocilium. **D:** Like cochlear hair cells, vestibular hair cells respond to stimulation with graded potentials. They do not fire action potentials. The hair cell releases glutamate from a specialized type of active zone called a **ribbon synapse** onto postsynaptic vestibular afferents. At rest (left), the stereocilia are in the neutral position (top row), the hair cell membrane potential is about -50 mV (middle row), and vestibular afferents have a resting discharge of 50–100 spikes per second (bottom row). In response to a stimulus that deflects the stereocilia in the preferred direction (middle), the hair cell depolarizes and releases more glutamate. Consequently, the vestibular afferent fires more rapidly. In contrast, in response to a stimulus that deflects the stereocilia in the nonpreferred direction (right), the hair cell hyperpolarizes and releases less glutamate than at rest. Consequently the vestibular afferent fires less rapidly. The depolarized rest potential in the hair cell and the resting discharge of the vestibular afferent enable the vestibular system to respond to stimulation in opposing directions.

Figure 19-6. **A:** In an upright person at rest, the otoconial mass of the sacculus is displaced downward due to the force of gravity. During linear accelerations in the vertical plane, the sacculus is displaced either farther downward during upward acceleration or upward during downward acceleration (**B**). When the sacculus floats up, as occurs during a downward acceleration, the resting effect of gravity on the sacculus is relieved momentarily, resulting in a feeling of “weightlessness.” **C:** The resting state of the utricular otoconial mass in an upright individual involves no displacement of stereocilia. However, during static tilt (**D**) or linear accelerations (**E**), the otoconial mass shifts, and the stereocilia are deflected. The deflection of the utricular stereocilia can be the same during a static tilt and a linear acceleration, as is the case in the examples illustrated in **D** and **E**. Additional input from the semicircular canals, somatosensory afferents, and motor centers are used by central vestibular neurons to disambiguate these signals. In both the sacculus and utriculus, there is a dividing line called the **striola** (red arrows in **A** and **C**). In the sacculus, the preferred direction of hair cells is always away from the striola, and in the utriculus, the preferred direction is toward the striola.



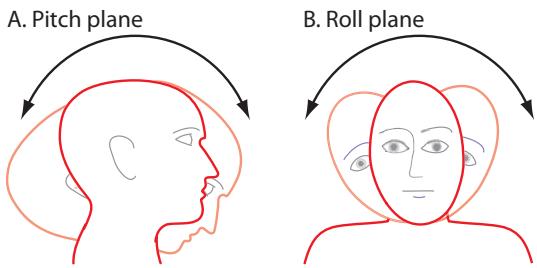


Figure 19-7. A: Rotations moving the head forward and backward as when nodding yes, or nodding off, are contained in the pitch plane. The center of rotation in the pitch illustrated is within the head. An example of an off-axis pitch would be the rotation involved in doing a handstand or flip. B: Side-to-side rotations of the head are contained in the roll plane, with the center of rotation located within the head. A cartwheel is an example of an off-axis roll rotation. Note that the yaw plane of rotation is illustrated in Figure 19-2A-B.

THE HEAD ROTATES IN THREE PLANES OF MOVEMENT

Head motion in a different plane of rotation is the stimulus for each of the three pairs of semicircular canals. To understand which rotations stimulate which semicircular canals, we need names for three planes of head rotation. The planes that we use are those used originally by farmers and seafarers and more recently by aviators. The **yaw** or horizontal plane of movement is described by moving one's head back and forth in the universal signal for "no" (Fig. 19-2A). The **pitch** plane is that in which the head moves when nodding; imagine a plow or a boat pitching forward (Fig. 19-7A). The third plane of head movement, the **roll** plane, is used when you lay your head to either side (e.g., on your shoulders; Fig. 19-7B). The nautical or aeronautic analogies, particularly for pitch and roll, are useful in imagining and remembering the three planes of rotational head motion.

ROTATIONS IN THREE ORTHOGONAL PLANES STIMULATE THE THREE SEMICIRCULAR CANAL PAIRS

As mentioned above, the key to inner ear function is transformation of the adequate stimulus into a stimulus of mechanical displacement that stimulates well-positioned hair cells. For semicircular canals, the transformation is accomplished by the fluid-filled tori oriented in three orthogonal planes. For our purposes, a fluid-filled torus attached to a rotating surface such as a "Lazy Susan" approximates a semicircular canal. Now, imagine that the torus is rotated clockwise. The fluid in the torus has inertia and stays stationary. Thus, the fluid moves in a counterclockwise direction *relative* to the torus walls (see Box 19-5). As simple as it sounds, the arrangement of a fluid-filled torus provides all that is necessary to transform angular motion into fluid movement. Fluid movement occurs in the absence of any angular motion in the case of *alcohol intoxication* (see Box 19-6).

In the inner ear, instead of a torus attached to a rotating tray, the membranous labyrinth is fixed within the bony labyrinth, which is fixed within the rotating head. The cristae and resident hair cells are located at the rostral end of the horizontal canals and are in a fixed position with respect to the head (Fig. 19-8). In addition to the pair of horizontal semicircular canals, there are bilateral posterior semicircular canals and anterior semicircular canals. The difference between the posterior, anterior, and horizontal semicircular canals is orientation (Fig. 19-8). The posterior and anterior semicircular canals are at right angles to each other and to the horizontal canals. Unlike the horizontal canals, the posterior and anterior canals do not sit within any one of the three planes described above: yaw, pitch, or roll. Instead, the orientation of the posterior and anterior canals is about equal parts pitch and roll,

Box 19-5

THE PRINCIPLE OF RELATIVE ENDOLYMPH MOTION WITHIN A CANAL IS EASILY DEMONSTRATED.

Fluid within a rotating torus stays stationary. Thus, the *relative motion* of the fluid is in the opposite direction from the rotation imposed upon the torus. If this idea does not make intuitive sense to you, a quick experiment may help. Fill a glass or a pot with liquid and place within the liquid anything that will float—a sprig of mint, an olive, an ice chip. Now rotate the container. You will see that the floating object stays stationary. The same principle operates within the semicircular canals. Rotation of a semicircular canal in one direction produces relative motion of the endolymph in the opposite rotational direction.

Now, imagine that instead of floating within the liquid, the mint stem was attached to the side of the glass. This arrangement would lead to the mint leaf bending in the direction of the relative motion of the fluid. In the same way, the stereocilia of canal hair cells bend in the direction of the relative motion of the endolymph.

so that the planes of the posterior and anterior canals are at 45-degree angles to the pitch and roll planes.

The horizontal canals form a pair because they are contained in a single plane (Fig. 19-8). Thus, a *pair* of canals is defined as two canals that share a plane of orientation. Using this definition, it is evident that the right anterior canal and left posterior canal are a pair (Fig. 19-8). They are contained in one plane that runs from a line that is 45 degrees between a rightward roll and a forward pitch to a line that is 45 degrees between a leftward roll and a backward pitch. Similarly, the left anterior canal and right posterior canal form a pair that is oriented in a plane that runs from a line that is 45 degrees between a leftward roll and a forward pitch to a line that is 45 degrees between a rightward roll and a backward pitch. Another way to visualize the orientations of the two vertical canal pairs is to view each pair as one stroke of an “X” through the center of the head.

ANGULAR ACCELERATIONS PRODUCE PREDICTABLE RESPONSES IN CANAL HAIR CELLS

In order to understand the consequences of rotational head movements, we need two more pieces of information: (1) the location of the ampullae in each canal and (2) the preferred direction of the hair cells in each canal. As illustrated in Figure 19-8, the ampullae are located at the anterior end of the horizontal and anterior canals and the posterior end of the posterior canal. The preferred direction of the hair cells is toward the utriculus for the horizontal canals and away from the utriculus in the cases of the anterior and posterior canals.

Now, we are ready to understand how canal hair cells respond to angular acceleration. We first consider a rotation in the yaw plane as the chain of events that leads from head rotation to hair cell responses is easiest to visualize and least cumbersome to describe.

In a clockwise rotation, also termed a rightward head movement (Fig. 19-9A) the bony and membranous labyrinths rotate clockwise, while the endolymph stays stationary (see Box 19-5). Since the crista and ampulla are anchored to and therefore move with the membranous labyrinth, endolymph moves in relation to these structures. In this way, clockwise head rotation sets up counterclockwise relative motion in the endolymph, which in turn deflects the cupula counterclockwise (Fig. 19-9B). Counterclockwise deflection of the cupula displaces the cupula toward the utriculus on the right and away from the utriculus on the left. As the preferred direction of the horizontal canal hair cells is toward the utriculus, horizontal canal hair cells on the right depolarize and horizontal canal hair cells on the left hyperpolarize.

As this example illustrates, all rotations in the yaw plane have opposing effects on hair cells in the left and right horizontal canals. This follows from the opposing rotational directions of endolymph in the left and right horizontal canals evoked by any rotation in the yaw plane. The same logic employed here can be applied to head rotations in planes other than yaw and to the responses of anterior

ALCOHOL INTOXICATION CAUSES VERTIGO BY CHANGING THE SPECIFIC GRAVITY OF THE CUPULA.

Normally, the cupula is neither heavier nor lighter than the endolymph. However, drinking alcohol dilutes the blood, so that it has a lower specific gravity than usual. If enough alcohol is consumed and the specific gravity of the cupula sufficiently decreased, the cupula will float up within the denser endolymph. Movement of the cupula deflects the stereocilia of hair cells in multiple canals. The pattern of hair cells that are stimulated depends on the position of the crista with respect to gravity, which in turn depends on head position. In any case, the pattern of hair cell responses is unlike any naturally occurring pattern. The central nervous system interpretation of the odd vestibular input is of a spinning motion, leading to a sense of vertigo.

The morning after alcohol intoxication, dehydration has set in and the specific gravity of blood is higher than normal. The endolymph, however, is a little less dense than usual, reflecting the state of the dilute blood when it was made, several hours earlier. So, now the cupula will sink in the endolymph, and the spinning sensation returns until blood and endolymph again become equilibrated to their normal specific gravities. Of course, one way to quickly achieve this equilibration is colloquially referred to as *the hair of the dog*, viz drink more alcohol, thereby lowering the specific gravity of blood, and in turn of the cupula.

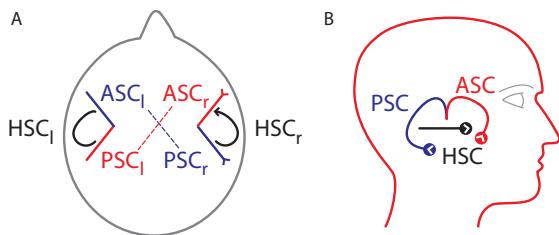


Figure 19-8. A: The horizontal semicircular canals on the left and right side (HSC_l and HSC_r) form a pair. This means that any rotation with a component in the yaw plane will have opposing effects on the two horizontal canals. The other two canal pairs are (1) the right anterior semicircular canal (ASC_r) and the left posterior semicircular canal (PSC_l) shown in red, and (2) the left anterior semicircular canal (ASC_l) and the right posterior semicircular canal (PSC_r) shown in blue. The arrowheads on the right side of the head indicate the location and orientation of the hair cells in the ampulla of each canal. The hair cells in the horizontal ampulla are oriented toward the utricle, whereas the preferred direction of hair cells in the anterior and posterior canals is away from the utricle. B: The location of the ampullae (filled circles) and the preferred direction of hair cells in each side semicircular canal (arrowheads) are illustrated on a side view of the right canals. From this perspective, it is clear that the lowest point in the vestibular apparatus is the ampulla of the posterior canal. Because of this topography, debris within the membranous labyrinth is thought to preferentially accumulate in the posterior ampulla (see Box 19-8).

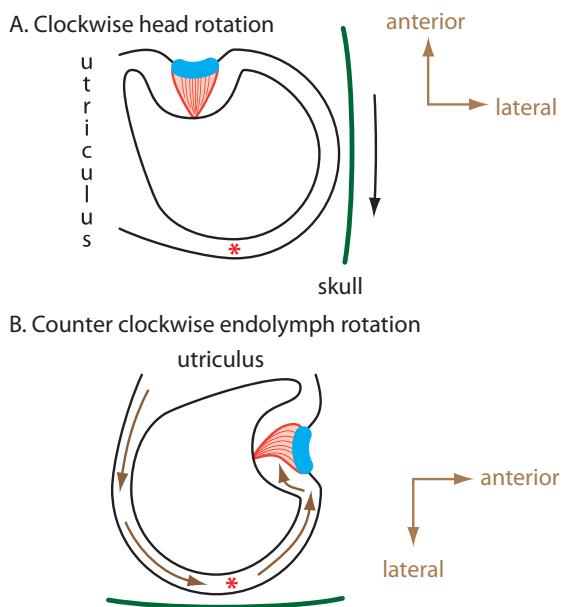
and posterior semicircular canals (see Box 19-7). There is also a shortcut to knowing the effect of any head rotation on any given semicircular canal. As it turns out, head rotations toward a canal's outer edge depolarize hair cells in that canal (see Table 19-1).

In **benign paroxysmal positional vertigo**, hair cells in a single canal or in multiple canals that cannot be activated together by natural head movements are activated (see Box 19-8).

THE UTRICULUS AND SACCULUS SENSE LINEAR MOTION IN ALL DIRECTIONS

The horizontally oriented utricle or **utricle** and the vertically oriented saccus or **saccule** are endolymph-filled chambers located in the vestibule between the semicircular canals and the cochlea. Recall that the stereocilia of the hair cells are embedded in the weighty otoconial masses which are displaced toward the Earth in response to gravity (Fig. 19-6A). Therefore, in an upright individual, stereocilia in the saccular macula are displaced downward, whereas the stereocilia in the utricular macula are not displaced (although they appear to be a bit squished, Figure 19-6C). Now consider the consequences of tilting the head to the side, a static roll of the head. The otoconial mass in the utricular macula is displaced downward and

Figure 19-9. A: The right horizontal semicircular canal, viewed in isolation from above, is diagrammed with anterior toward the top of the page and lateral to the right. During a clockwise head acceleration (A), the bony and membranous labyrinths rotate clockwise while the endolymph stays stationary. This means that endolymph located at a given point (red asterisk in A) is located in the same place in space (red asterisk in B), even after the surrounding structures have moved. As the crista and ampulla are anchored to the membranous labyrinth, endolymph moves relative to these structures. The relative motion (brown arrows) of the endolymph with respect to the crista and cupula deflects the cupula, which leads in turn to the deflection of the stereocilia of the hair cells. In the rotation illustrated, the stereocilia are deflected toward the utricle, which is the preferred direction of hair cells in the horizontal canals. Thus, a clockwise or rightward acceleration results in the depolarization of right horizontal hair cells. The same logic used here can be employed to deduce the effect of any rotational acceleration.



Box 19-7

THE PREFERRED DIRECTION OF EACH CANAL CAN BE DEDUCTED BY KNOWING THE LOCATION OF THE CRISTA AND THE PREFERRED DIRECTION OF HAIR CELLS.

It is important to know which end of each canal contains the ampulla. All hair cells are depolarized by movement of the cupula in one direction and inhibited by cupular deflection in the opposite direction. By knowing the location of the ampullae and the orientation of the hair cells in each canal, the effect of any head rotation on the hair cells in any of the canals can be deduced by those interested in doing so. As explained in the text, there is also a shortcut method to remembering the effect of any head rotation on hair cells in each canal.

The ampullae of the anterior semicircular canals are located at the rostral end of the canals, and the preferred direction of the hair cells is *away* from the utricle. This means that a rotation that is half-pitch forward and half-roll right maximally stimulates right anterior canal hair cells. This same rotation is orthogonal to the preferred direction of hair cells in the left anterior canal. Therefore, hair cells in the left anterior canal are not affected by a

rotation in the preferred direction of the hair cells in the right anterior canal.

The ampullae of the posterior canals are located at the caudal end of the canals, and hair cells are oriented away from the utricle. A rotation that is half-pitch forward and half-roll right causes relative motion of endolymph in the left posterior canal toward the utricle (Fig. 19-8). Deflection of the posterior canal cupula toward the utricle, the non-preferred direction, leads to hyperpolarization of the hair cells. Thus, a rotation that is half-pitch forward and half-roll to the right depolarizes hair cells in the right anterior canal and hyperpolarizes hair cells in the left posterior canal. Using the same logic, the reader can work out the sequence of events that leads from a rotation that is a half-pitch forward and half-roll to the left to the depolarization of hair cells in the left anterior canal and hyperpolarization of hair cells in the right posterior canal.

TABLE 19-1. THE EFFECT OF ROTATIONS IN EACH OF THE THREE PLANES ON HAIR CELLS IN EACH CANAL PAIR IS LISTED

ROTATION	L/R HORIZONTAL	L ANTERIOR	R POSTERIOR	R ANTERIOR	L POSTERIOR
Yaw	Ipsilateral depolarization Contralateral hyperpolarization	No effect		No effect	
45° pitch forward + 45° roll rightward	No effect	No effect		Forward depolarization Backward hyperpolarization	Forward hyperpolarization Backward depolarization
45° pitch forward + 45° roll leftward	No effect	Forward depolarization Backward hyperpolarization	Forward hyperpolarization Backward depolarization	No effect	

For each plane, the effect of movement in each direction is listed. For example, rotation backward in the half pitch and half right roll plane is listed as a backward rotation. An ipsilateral yaw rotation refers to a rotation of the nose toward the side of the horizontal canal. L: left, R: right

Box 19-8

BENIGN PAROXYSMAL POSITIONAL VERTIGO IS THOUGHT TO RESULT FROM DISLODGED OTOCONIA FLOATING INTO THE SEMICIRCULAR CANALS.

Benign paroxysmal positional vertigo is thought to result when some part of the otoconial mass dislodges from its position above the macular hair cells and floats into the canals. The displacement of endolymph stimulates canal hair cells, resulting in a perception of head rotation. Since the posterior canal is the lowest part of the labyrinth when the head is in an upright position, the dislodged fragments from an otoconial mass tend to move there, particularly during shifts in head position.

The input from stimulation of one canal is not matched by any other input. There is no input from the stimulated canal's partner (the other canal in the pair), nor does visual input match the errant canal input. For example, depolarization of hair cells in the right posterior canal without hyperpolarization

of hair cells in the left anterior canal would not occur normally. The result is a sudden, or paroxysmal, feeling of vertigo that is often accompanied by nausea.

Benign paroxysmal positional vertigo can be caused by head trauma or even by riding a roller coaster. In many cases, a cause cannot be identified. Treatment is aimed at moving the head so that the otoconial mass fragments move from the canals to the vestibule containing the utriculus and sacculus. Since the macular hair cells are embedded in the otoconial mass, they do not respond to free-floating otoconia. With time, benign paroxysmal positional vertigo typically subsides, presumably as the free otoconia are resorbed.

toward the side of the tilt (Fig. 19-6D). Using these principles, it is clear that every position of the head, either upright or tilted, evokes utricular responses.

The saccus and utriculus also respond to linear accelerations of the head caused by self-motion, falling, or vehicular movement. During linear accelerations, the heavy otoconial mass lags behind the macula, so that the hair cell stereocilia are displaced. For example, accelerating forward will cause the utricular otoconial mass to lag backwards, bending the stereocilia backwards as well (Fig. 19-6E). During an upward acceleration, as occurs during the upward phase of a jump, the otoconial mass lags behind below. Conversely, on the downside of a jump, the otoconial mass lags behind *above* the macula (Fig. 19-6B). By sensing the displacement of the otoconial mass induced by gravity and other linear accelerations, hair cells in the utriculus and saccus signal both the static position of the head and linear accelerations of the head.

HAIR CELLS RESPOND TO ACCELERATION BUT CODE FOR VELOCITY

Vestibular hair cells only respond to changes in acceleration and not to changes in velocity. In the canals, the cupula is only deflected by movement of the endolymph, and endolymph only moves during angular acceleration of the head. However, movement of the endolymph in the canals is opposed by frictional forces arising from the viscosity of the endolymph and the elasticity of the cupula. These opposing forces cause the movement of the endolymph and cupula to lag head acceleration and to approximate the velocity of the head. Thus, the receptor cells require head acceleration to detect movement of the cupula but code for **head velocity**. Another way to view this is that the lag of the endolymph and cupula integrate the acceleration stimulus into a velocity signal. Similarly, macular hair cells in the otoconial organs only respond to linear accelerations, but have responses that are proportional to velocity.

That hair cells only respond to acceleration is evident by the lack of any vestibular sensation during constant velocity motion, such as occurs in a car or a plane cruising at a constant speed. In contrast, during takeoff and landing of a plane and during car accelerations and decelerations, a clear sensation of slowing down or speeding up is perceived.

VESTIBULAR END ORGANS ARE STIMULATED BY ACCELERATION IN THE PLANE OF THEIR ORIENTATION

Under normal circumstances, head movements rarely adhere neatly to the planes of the three canal pairs. In response to natural movements that include rotational components in the orientation of more than one canal pair, the composite movement is decomposed into its vector components. For example,

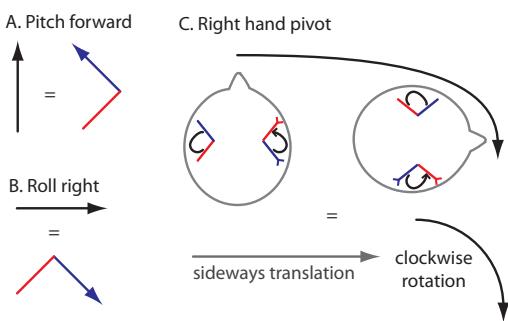


Figure 19-10. The vestibular system operates by decomposing every movement into the components contained within the planes of the canal pairs, the utriculi and the sacculi. Three examples are illustrated. **A:** A pitch forward (black arrow) is equal parts forward movement in the right anterior semicircular canal—left posterior semicircular canal plane (red) and forward movement in the left anterior semicircular canal—right posterior semicircular canal plane (blue). **B:** A roll right (black arrow) is equal parts forward movement in the right anterior semicircular canal—left posterior semicircular canal plane (red) and backward movement in the left anterior semicircular canal—right posterior semicircular canal plane (blue). **C:** Natural head movements typically involve both angular and linear acceleration. The same principle of decomposition applies here. The rightward pivot illustrated is composed of a rightward translation and a clockwise rotation. These movements evoke responses in hair cells in the utriculi and the horizontal semicircular canals.

a pitch forward is equal parts forward movement in the plane of the left anterior-right posterior canal pair and in the plane of the right anterior-left posterior canal pair (Fig. 19-10A). As another example, a roll right is equal parts forward movement in the right anterior-left posterior canal pair plane and backward movement in the left anterior-right posterior canal pair (Fig. 19-10B). Application of this type of movement decomposition into component vectors can be extended from exclusively rotational movements to truly natural head movements, which are likely to include both linear and angular acceleration (Fig. 19-10C).

VESTIBULAR AFFERENTS RESPOND TO ACCELERATION IN THE PREFERRED AND NONPREFERRED DIRECTIONS

In response to release of glutamate from hair cells at rest, vestibular afferent neurons discharge at fairly high rates, in the range of 50–100 spikes/second. Hair cell hyperpolarization, as occurs with accelerations in the nonpreferred direction, decreases excitation of afferents and therefore the rate of afferent firing (Fig. 19-5D). Of course, depolarization of hair cells results in more glutamate release from hair cells and a greater discharge release in vestibular afferents.

Thus, the elevated resting potential of hair cells and resting discharge of vestibular afferents permits bidirectional responses.

THE VESTIBULAR NUCLEI INTEGRATE NONVESTIBULAR INPUTS WITH VESTIBULAR AFFERENT INPUT

Vestibular afferents project to neurons in the four vestibular nuclei of the brainstem (see Chapter 12). Under many conditions, the responses of vestibular nucleus neurons to head movements reflect the responses of vestibular nerve afferents. However, there are several exceptions to this general rule. Notable exceptions include:

- Vestibular nuclear neurons have a larger response to very slow accelerations than do vestibular afferents. The greater response of central neurons is due to input from visual pathways. The summation of visual and vestibular inputs used to interpret slow accelerations means that slow accelerations of either self or the world can be easily misinterpreted. A common example of this is experienced when sitting in a smoothly moving vehicle such as a train. The perception when sitting in a still train and viewing another train slowly

accelerate is difficult to distinguish from the perception of viewing a train that is not moving while sitting in a slowly accelerating train.

- The saccular and utricular responses to head tilt and linear translation can be the same (Fig. 19-6D–E). For example, lying supine and accelerating forward stimulate the sacculus and utriculus identically. In essence, the ambiguity arises because at the level of the macular stereocilia, accelerations due to gravity and those due to translational movement are indistinguishable. However, the responses of vestibular nuclear neurons to tilt and translation differ, as indeed do our perceptions of the two stimuli. Information from somatosensory afferents, including proprioceptive signals, and motor centers (see below) may be of particular importance in making such distinctions.
- During self-generated movements that produce head movements, expected vestibular inputs are suppressed (see Box 19-9). This cancellation of expected sensory input is very similar to the situation that occurs in the somatosensory system (see Chapter 18).

Fundamentally, the responses of vestibular nuclear neurons differ from those of vestibular afferents because of the large number and variety of *nonvestibular* inputs to vestibular nuclear neurons. In addition to receiving input from primary vestibular afferents, vestibular nuclear neurons receive:

- *Visual input including input from midbrain visual nuclei carrying information about motion of the entire visual field, termed optic flow:* The movement of the whole visual field as one rides in a moving vehicle is an example of optic flow.
- *Information about eye position and eye movements:* This information is used to interpret visual input.
- *Proprioceptive inputs from neck muscles:* Proprioceptive input from muscle and joint receptors provides information about the position of the neck.
- *Somatosensory inputs such as cutaneous mechanoreceptors:* The amount of pressure from the body's contact with surfaces changes with head and body acceleration. One common example is the elevated pressure felt on the back during forward accelerations in a vehicle. A dramatic example of this is the extreme pressure exerted on astronauts during rocket blast-off.
- *Motor command inputs:* Sensory inputs that are expected to result from the movements that we make are cancelled. Information from motor centers about current movements allows this cancellation to occur. In addition, motor signals may disambiguate the information from the utriculi. For example, head tilt is accompanied by standing, an active movement (see Chapter 23), whereas linear acceleration is often the product of running, walking, or the like. The sources of the movement-related cancellation signal are not known but likely arise at least in part from the cerebellum.

Outputs from the vestibular nuclei target motor-related regions that are critical to controlling eye movements and postural balance. Projections to the oculomotor,

MOTION SICKNESS IS A MODERN AFFLICION BORNE OF VEHICULAR TRAVEL.

Throughout evolution, adult terrestrial animals have traveled only when self-propelled. In the last few thousand years, this situation changed as humans invented boats, trains, automobiles, and then planes, all of which are now routinely used to convey human passengers across long distances. Of course, the vestibular system has not evolved to catch up with the recent development of passenger vehicles.

In the absence of a motor signal that allows for cancellation of anticipated sensory inputs, rapid translational movement elicits responses in central vestibular neurons. For example, consider traveling through urban streets, replete with pot holes, during the stop-and-start traffic of rush hour. Much of the vestibular stimulation inherent in traveling this course would be canceled by a person walking or running through the streets. However, when a person traverses this same terrain as a passenger in a city bus, innumerable accelerations and decelerations in both vertical and horizontal planes gain access to central vestibular neurons. Consequently, the overall message from the vestibular system is one of head motion, and lots of it. Now, consider that the bus passenger is reading a book while sitting on the bus. The image of the book type remains steady, thanks to the vestibuloocular reflex (see Chapter 26). Thus, there is a mismatch between

information from the vestibular system—lots of movement—and information from the visual system—the world is steady.

Currently, sensory mismatch is thought to cause motion sickness. When traveling on earth, the mismatch involved is primarily between visual and vestibular signals, as above. In space, mismatch between the various vestibular end organs occurs because of the microgravity environment. The toxin detector hypothesis holds that across evolutionary time, sensory mismatch occurred in response to ingested neurotoxins and that consequently, the adaptive reaction of nausea and emesis, or vomiting, evolved. Although everyone can experience motion sickness given severe enough conditions, some are more susceptible than others; the reason for the variation in susceptibility is not known.

The nonpharmacological strategy to avoid motion sickness focuses on avoiding near fixation during passenger travel. The moving visual image is thus more in line with the vestibular input of motion. The most common pharmacological treatment for motion sickness is scopolamine, a muscarinic receptor antagonist, which reduces gastrointestinal motility. Scopolamine also blocks accommodation, nasal and oral secretions, and causes some degree of drowsiness.

trochlear, and abducens nuclei, which control the extraocular muscles (see Chapter 10), serve reflexive eye movements. Projections to the cervical ventral horn are important in coordinating head and shoulder movements and thus gaze with head motion. Projections to the spinal ventral horn at all levels are critical to maintaining postural balance. Additional projections to the cerebellum also contribute to the coordination of postural balance and eye movements with head position and motion.

VESTIBULAR PATHWAYS INFLUENCE AUTONOMIC FUNCTION

Vestibular pathways reach regions near the head region of somatosensory cortex via the ventral posteromedial nucleus of the thalamus. Stimulation within “vestibular” cortical areas most frequently produces a sense of

movement or dizziness. Vestibular pathways also reach insular cortex. Vestibular information in the forebrain likely serves two primary purposes. First, vestibular information is critical to spatial orientation and the sense of self in space. Second, vestibular information appears key to a sense of bodily well-being. The comorbidity, or coincidence, of anxiety disorders and symptoms reflective of vestibular dysfunction—dizziness, vertigo, disequilibrium, and nausea—may result from the strong influence of vestibular inputs on emotional and homeostatic systems.



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SECTION 5: MOTOR CONTROL

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CHAPTER 20

MOTOR CONTROL

THE MOTOR SYSTEM WORKS WITH SENSATION, HOMEOSTASIS, AND COGNITION TO PRODUCE UNIFIED AND COHESIVE BEHAVIOR

Before embarking on our journey from skeletal muscle contraction to action, we explicitly recognize that *movement is interdependent with sensory, homeostatic, and cognitive brain function*. A few examples should suffice to convince you of the necessary interactions between motor control and sensory, homeostatic, and cognitive function.

Without sensory inputs, people would stumble hesitatingly about the world, hurt themselves, and live short lives. Afferents from skeletal muscles and skin are so critical to the skeletal motor system that we include them as part of the motor system even though they are somatosensory afferents—embryologically, anatomically, and physiologically—rather than motoneurons. The relationship between movement and sensation goes both ways. As exemplified by the middle ear musculature, some skeletal muscles serve primarily to modify perception rather than to exert forces on the outside world. Even beyond this somewhat unique example, what we see and hear is clearly determined by the direction that we are facing, whether we are moving, and a myriad of other factors directly under the control of skeletal muscles.

The connections between homeostasis and skeletal movement are myriad. When walking, and even more so when running, autonomic changes in cardiac output, **vasomotion** (see Box 20-1), and sweating allow one to continue without either fainting or overheating. These examples make clear that *skeletal muscles alone cannot accomplish our goals as we move through the world*. Similarly, autonomic control of smooth and cardiac muscle cannot keep the body in homeostasis without the participation of skeletal muscles that support breathing, thermoregulation, and other necessary functions. Accommodation, micturition, and mating all require both skeletal and smooth muscle participation, revealing the somewhat artificial divide between somatomotor and autonomic movements.

All movements proceed upon a platform that depends entirely on motivation, mood, and thought. Most fundamentally, without motivation—either conscious or unconscious—we simply do not make voluntary movements. The converse also holds: communicating motivation, mood, and thought depends absolutely on the final common currency of skeletal muscle excitation. This statement is essentially a tautology as we derive all that we know about cognitive function from the contraction of skeletal muscles. The manner in which a person walks, stands, writes, and speaks depend absolutely on skeletal muscle excitation. *Movements borne of muscles inform us of who a person is and are in fact the only clues we have as to the nature of*

VASOMOTION IS AN UMBRELLA TERM FOR BOTH VASODILATION AND VASOCONSTRICCTION.

Vasomotion refers to changes in blood vessel diameter due to the contraction or relaxation of smooth muscle surrounding the vessel. Cutaneous vasoconstriction reduces blood flow and increases blood pressure, whereas vasodilation has the opposite effects. Typically, the brain controls vasomotion in different vascular beds independently and according to the demands of the task. For instance, when a person is running away from danger, arterioles to skeletal muscles in the legs dilate and those to the digestive tract constrict, supporting escape now and digestion later.

a person's inner self. We instantly recognize a stranger as uptight, mellow, or depressed, words which, although they describe abstract traits of personality and affect, derive from, and readily conjure up physical images. Because of the interdependence of self and movement, we feel that we know public figures and have a sense whether we would like them or not, simply after watching their *movements* in films or on television, all without ever exchanging words or coming face to face.

Despite the extensive interdependence of motor, sensory, homeostatic, and cognitive systems, we can identify neural circuits that are particularly central to movement and action. In the next six chapters, we focus on these key motor circuits.

TO MOVE SMOOTHLY AND AT WILL PRESENTS A BIG CHALLENGE

The brain faces an incredible challenge in creating the full range of motion that humans are capable of and producing movements at the appropriate and desired times. The muscles that are involved in even a simple motion, for example turning the palm upward, are numerous and act at several joints (digits, wrist, and elbow). Motor command must be further adjusted to account for muscle fatigue, balance, and weight, or *load*. The specific forces and muscles required to turn the palm upward will be different in the water or in the air, when supine, prone, or upright, when carrying a heavy bag versus being load-free. An unanticipated protruding tree root across the path or a bee sting requires adjustments to keep planned movements “on track” while avoiding injury and maintaining balance. Yet, in most cases, the motor system is able to anticipate and avoid impediments to reaching motor goals rather than correcting an action only after a motor blunder. Visual, auditory, tactile, and vestibular information, together with past experiences, are used by the brain to coordinate complex motor strategies with the best chance of achieving the intended goal.

VOLUNTARY ACTION DEPENDS ON A SUBSET OF ALL MUSCLES, THE SKELETAL MUSCLES

The body contains *smooth* and *striated* muscles. Smooth muscle has a histologically smooth appearance and is controlled automatically rather than voluntarily. Two types of muscle contain visible striations of actin and myosin: *cardiac* and *skeletal*. Cardiac muscle resembles smooth muscle in that it cannot be controlled consciously but differs from smooth muscle in its lightly striped appearance. *Skeletal muscle can, in general, be controlled purposefully* and is the subject of this section.

Although skeletal muscle supports purposeful movement, we are incapable of willfully contracting most skeletal muscles *in isolation*. Instead, we contract most

skeletal muscles as part of a group. For instance, when pulling a door open, our biceps muscle contracts along with a number of other muscles in the arm, shoulder, trunk and even legs. In another example, we have exquisite control over laryngeal muscles, allowing us the power of vocalization, but we cannot willfully contract or relax a single laryngeal muscle, such as the left oblique arytenoid muscle. Some skeletal muscles, such as the stapedius and tensor tympani are simply not available for voluntary control, even as part of a group. Many muscles that can be controlled voluntarily are also controlled unconsciously. For example, the diaphragm, a skeletal muscle critical to breathing, continues to contract rhythmically during sleep or general anesthesia and can also be willfully controlled as when we intentionally take a deep breath.

The term *skeletal muscle* is used because most noncardiac striated muscle attaches, at least at one end, to a bone. Of course, there are exceptions to this rule, just as there are exceptions to the “skeletal-muscle-is-voluntarily-controlled” rule. Exceptions include several muscles of facial expression that attach only to skin, intrinsic laryngeal muscles that attach to cartilage, as well as muscles that surround or attach to the trachea, esophagus, and urethra. Nonetheless, throughout this book, I employ the imperfect shorthand of referring to all noncardiac striated muscle as skeletal.

MOVEMENT CAN BE VERY FAST BUT INFLEXIBLE OR SLOWER AND CONTROLLED

Movements are characterized as either **ballistic** or controlled. Ballistic movements are projectile in the old-fashioned, pre-“smart bomb” sense. After movement initiation in a particular direction and with a given force, no additional steering or guidance of a ballistic movement occurs. Common examples include fast eye movements called *saccades* (see Chapter 26), swinging a bat, or throwing a punch. In contrast, smooth, controlled movements may start with one trajectory but that trajectory may be altered during the course of the movement, just as a “smart bomb” changes heading to hit an evasive target. Examples of controlled movements include watching a bird fly across the sky, threading a needle, peeling an apple, and caressing a loved one.

In general, ballistic movements utilize axial and proximal limb muscles and can be initiated reflexively, automatically, or voluntarily. Most controlled movements use proximal and distal limb muscles and are controlled through a constant dialogue with the brainstem and cerebral cortex. Many muscles, such as the extraocular muscles, support both ballistic and controlled movements. Axial movements can be controlled as well as ballistic. Examples of controlled axial movements abound in dance.

Ballistic movements offer the major advantage of being very fast. However, speed comes at the cost of flexibility and accuracy: if the expected target location changes after the aim-fire sequence initiates, the movement will end up off target. Even when a target remains stationary, ballistic movements are often less accurate than controlled ones. Although controlled movements are far more flexible and often more accurate than ballistic movements, they are also far slower. Supporting flexible

behavior is neurally more complicated than supporting fixed behavior. Therefore, the brainstem and cerebral cortex generate controlled movements, whereas simpler circuits in the brainstem and spinal cord can generate ballistic movements.

THE MOTOR HIERARCHY MAKES ACTIONS OUT OF MUSCLE CONTRACTIONS

As introduced in Chapter 1, skeletal muscles cannot contract independently, without input from the central nervous system. They only contract in response to action potentials fired by innervating motoneurons. Even when a motoneuron fires an action potential and a muscle contracts, the result is a *twitch*, the simplest of movements. Although a twitch is a physical movement, it is certainly not a useful or natural one. The motor hierarchy uses twitches as building blocks and organizes the timing, strength, and distribution of muscle contractions to produce *movements*, ranging from simple to complex (Fig. 20-1). The lowest elements of the motor hierarchy, local circuits in the ventral horn involving motoneurons and motor interneurons, support the simplest movements, such as flexions or extensions of a single limb. Activity in sensory afferents from both muscle and skin reaches these local circuits to elicit quick reflexive adjustments.

Within the spinal cord and brainstem, **central pattern generators** produce the basic motor components involved in far more complex movements such as walking, maintaining an upright posture, breathing, or swallowing. *Central pattern generators are circuits of neurons that create a patterned sequence of motor activity and can do so in the absence of peripheral feedback* (see more in Chapter 22).

Brainstem motor control centers, such as the red nucleus (see Chapter 12), employ circuits in lower parts of the motor hierarchy to produce fairly complex movements, such as ingestion or locomotion. However, these movements have no meaning. They resemble the movements that result from motor cortex stimulation in awake neurosurgical patients. Recall that in response to electrical stimulation of the motor cortex, patients report that a body part moved or “could not move” or that the body part “wanted” to move (see Box 15-1). In these reports, the body part rather than the person is the *actor*: they do *not* report

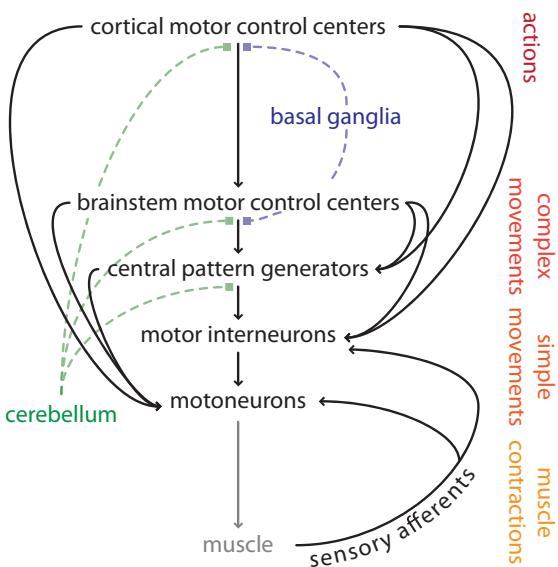


Figure 20-1. The motor hierarchy (black) consists of connections from higher motor centers to lower motor centers and ultimately to motoneurons, the final common pathway controlling skeletal muscle. Motoneurons are capable of producing muscle contractions. Simple circuits involving motor interneurons can produce simple movements, whereas central pattern generators and brainstem motor control centers produce complex movements such as chewing, walking, and the like. Cortical circuits imbue movements with meaning and thus produce actions. Feedback from primary somatosensory afferents that innervate the muscles and joints reaches motoneurons and motor interneurons directly. All other sensory input to motor areas is indirect (not shown). The motor hierarchy is marked by projections from higher motor centers to all lower motor areas. The two major motor modulatory regions—the cerebellum and the basal ganglia—modulate higher motor centers but do not directly connect to motoneurons.

“I moved my hand.” This distinction is key to the contribution of the cerebral cortex. The cerebral cortex is required to make movement personal, to transform physical movement into a physical expression of the self. Movement so imbued with personal meaning and motivation is termed *action*. We even personalize reflexes, “I saw the ball coming and I just put up my hand.”

Since the brain adds meaning to movements, two different actions can share the same component movements. For example, a smile of enjoyment, a smile used as a greeting, and a smile in response to a command during a game of Simon Says all share a similar up-turning of the mouth. Yet, these three smiles are three different actions, each occurring in a different context. The context depends on the brain. Nerves and other peripheral structures do not “do” context. Therefore, *context-specific* impairment is pathognomonic or diagnostic of a central nervous system lesion.

TWO MODULATORY LOOPS ARE CRITICAL TO SMOOTH, RECOGNIZABLE MOVEMENTS

The motor hierarchy does not and cannot produce recognizable human motion without running its motor plan through two neural loops that provide indirect and modulatory input back to the motor hierarchy (Fig. 20-1). These two regions serve critical motor functions:

- The *cerebellum* smoothes, coordinates, and sequences movements and is required for motor learning
- The *basal ganglia* suppress most movement most of the time, and also select which movements to make when, often chaining together several actions into one seemingly unitary action

Both modulatory regions modulate motor centers in the brainstem and forebrain rather than exerting effects directly on either motoneurons or motor interneurons. The importance of the cerebellum and basal ganglia in generating the smooth movements that humans make, movements that involve multiple muscles, joints, and limbs and take place over the course of minutes or even hours, cannot be overestimated. Indeed, several of the most common motor disorders are disorders of the cerebellum or basal ganglia.

DIFFERENT TYPES OF MOVEMENT OPERATE, AS WELL AS FAIL TO FUNCTION, INDEPENDENTLY

Consider the consequences of damage to a cerebral motor control center. We use a simple example—the frontal eye fields—which organize gazes to the contralateral side, so that an individual with damage to the right frontal eye

field cannot make a willful saccade to the left. Does this mean that this person cannot abduct the left eye under any circumstances? Absolutely not: this person still makes reflexive movements to the left and still orients to a rapidly moving stimulus streaking to the left. In contrast, a person with an injury to the right abducens nerve cannot abduct the right eye under any circumstances. As this example illustrates, *different actions employ overlapping but not identical motor pathways, all of which funnel through the common pathway of the motoneuron.* Therefore, dysfunction of any central motor region above the level of the motoneuron affects one or more, but not all, types of movements.

The movement types that we recognize and will discuss are:

- *Passive movement* occurs without any neural input, as for example when a physician bends the arm about the elbow or during a stretch produced by active contraction of an antagonist muscle. A deficit in passive movement is commonly felt by the physician as a resistance against imposed movement. Deficits in passive movement are caused by central rather than peripheral nervous system lesions. Lesions in the basal ganglia produce **rigidity**, whereas lesions of descending motor tracts cause **spasticity**.
- *Reflexes* are very simple movements, such as flexion withdrawals from a painful stimulus. Reflexes are relatively unaffected by voluntary control. An absence of reflexive movement, termed **areflexia**, is caused by impairment of motoneurons or the connection of motoneurons to muscles. A condition of *exuberant* reflexes, termed **hyperreflexia**, typically results from lesions of descending motor tracts. Hyperreflexia is discussed in Chapter 23.
- *Stereotyped, semiautomatic movements* include rhythmic behaviors, such as chewing, walking, and swimming, as well as nonrhythmic ones such as vomiting, micturition, and even postural control, which depend on central pattern generator circuits. Central pattern generator circuits and their component neurons are critical to producing the basic pattern of stereotyped movements.
- *Self-generated actions* include a large variety of motions that we initiate (see Box 20-2). Self-generated actions may occur in response to a stimulus—gazing at a beautiful painting or gasping at a story told by a friend. Yet, unlike a reflex, a self-generated action is far removed from sensory input in terms of both time and neural distance traveled. Self-generated movements are heterogeneous but fall primarily into two motivational categories:
 - A subset of self-generated actions are *volitional* or *voluntary actions*, also called *willful*, *purposeful*, or *deliberate* actions. Volitional actions require the participation of the cerebral cortex. Moving in response to a command, as occurs during a game of Simon Says, is an example of a voluntary and conscious movement. Voluntary actions account for a minority of our skeletal muscle contractions. An absence of voluntary movement is commonly termed **paralysis**. An impairment of voluntary movement alone, meaning that nonvolitional self-generated actions are normal, is termed *volitional paresis* (Fig. 20-2).

Box 20-2

WE USE THE TERM
SELF-GENERATED TO
REFER TO COMPLEX,
PURPOSEFUL
MOVEMENTS.

Although acknowledging that reflexive movements result from the activity of motoneurons and other central neurons, just as semi-automatic, emotional, and voluntary movements do, I will use the term **self-generated** only in reference to the latter movement types.



Figure 20-2. The facial expressions of a patient with a lesion in the left supplementary motor area at rest (A), in response to a verbal command (B), and during natural emotional states (C–D) are shown. **A:** The facial expression at rest is symmetrical and normal. The nasolabial folds are symmetrically apparent in this patient in contrast to the patients with Bell's palsy illustrated in Figure 10-10. **B:** In response to a request to show her teeth, the left side of the patient's face moves normally, but there is little change in the right side of the face. **C–D:** During feelings of enjoyment and annoyance, the patient makes symmetrically normal facial expressions of emotion. Impairment of volitional facial expressions coupled with intact emotional facial expressions is termed *volitional facial paresis*. Note that, in this patient, impairment of movement is *context-specific*, accompanying volitional but not emotional facial expressions. Context-specificity is pathognomonic for a central nervous system lesion. In contrast, Bell's palsy, due to a peripheral lesion, impairs all movements of the ipsilateral face, regardless of context.

Photographs kindly provided by Adrian Danek. Additional information about this patient's case is available in Jox et al., 2004.

- Most self-generated movements are *emotional actions* initiated for reasons that often do not reach consciousness. We may assign a post hoc reason, often inaccurate, to the occurrence of emotional actions. Pathways from the cerebral cortex to motoneurons that are critical to producing emotional actions are distinct from the pathway required for voluntary actions. *Our emotional actions reflect our true feelings far more accurately than do our verbal explanations, underscoring the inherent honesty of the emotional motor system.* An inability to perform emotional actions accompanied by intact volitional action is termed *emotional paresis* or *amimia* (Fig. 20-3).

The terms *paralysis*, *paresis*, and *–plegia* are ambiguous with respect to motor pathways involved. Anyone with a lesion or complete dysfunction in the motoneuron, neuromuscular junction, or muscle is clearly paralyzed and cannot contract the affected muscle under any context. This type of paralysis is termed **flaccid**, as the muscles have no tone and never contract. In contrast, the paralysis caused by a lesion in the corticospinal pathway or supplementary motor area, involves the inability to move in response to a verbal command. Patients with this type of paralysis, which is typically termed **spastic** paralysis, have hyperreflexia (see full discussion in Box 23-1). These patients may even be able to generate emotional movements, as is true of the patient illustrated in Figure 20-2. It is important to understand that despite sharing a common moniker, the two forms of paralysis are not equivalent. Stereotyped and emotional actions are relatively spared and reflexes are actually enhanced after lesions of tracts descending from motor cortex, whereas all types of actions are obliterated by motoneuron lesions.

The terminology used to describe patients who do not move is further complicated by **akinesia**, a disorder resulting from damage to basal ganglia circuits. Akinesia is a prominent symptom in patients with severe Parkinson's disease. Akinetic patients

A. Smile in response to a command



B. Smile in response to a funny joke



Figure 20-3. This young patient with *emotional facial paresis* smiles normally in response to a command but fails to smile symmetrically in response to a funny joke. This patient has essentially the reverse condition from that of the patient illustrated in Figure 20-2. Yet, like the patient illustrated in Figure 20-2, this patient has a context-specific impairment, automatically implicating a lesion *within* the central nervous system. Although volitional facial paresis is typically the result of lesions of the corticospinal tract or supplementary motor area, lesions that give rise to emotional facial paresis are more widespread. In this patient, the lesion is in the striatum and anterior internal capsule on the left side, contralateral to the side of impaired emotional movement.

Reprinted from Trosch, R.M., et al. Emotional facial paresis with striatocapsular infarction. *J Neurol Sci* 98: 195–201, 1990, where more information about this case is available, with permission of the publisher, Elsevier.

do not move much at all either for internal motivational reasons or in response to a voluntary command. However, they *can* move as *there is absolutely nothing wrong with the motor hierarchy*. Reflective of a healthy motor hierarchy, akinetic patients make relatively normal visually guided and reflexive movements.

In the next several chapters, we explore the function of the motor system with an eye to understanding clinical presentations such as those illustrated in Figures 20-2 and 20-3. We start at the lowest level of the motor hierarchy—the muscles and motoneurons—before working our way up to the motor control centers and then to the motor modulatory regions.



ADDITIONAL READING

Holstege, G. Emotional innervation of facial musculature. *Move Dis* 17 (Suppl 2): S12–16, 2002.

Jox, R., Bruning, R., Hamann, G., and Danek, A. Volitional facial palsy after a vascular lesion of the supplementary motor area. *Neurology* 63: 756–7, 2004.

Trosch, R.M., Sze, G., Brass, L.M., and Waxman, S.G. Emotional facial paresis with striatocapsular infarction. *J Neurol Sci* 98: 195–201, 1990.

CHAPTER 21

THE MOTOR UNIT AND ORDERLY RECRUITMENT

MUSCLES VARY IN FORCE, SIZE, SPEED, AND ENDURANCE

Different movements require different physical feats and to accommodate this variety, the basic physiological features of different muscles vary. In other words, one muscle type does not fit all movements. The physical requirements of elevating the eyelid for the better part of a day differ from those of yanking open a door. Hand muscles used to hold and direct a pencil for writing differ from the diaphragm, which supports breathing, whispering, singing, and shouting. *Fine and coarse movements with different requirements for maximal force, speed of contraction, and resistance to fatigue are controlled differently by the brain and also utilize muscles that differ in their basic properties.*

THREE PRINCIPAL TYPES OF MUSCLE FIBERS DIFFER IN THEIR CONTRACTILE PROPERTIES

Our bodies' skeletal muscles support varied movements ranging from the steady opposition to gravity required to stand to the fast push-off needed for track and field competition and the meticulous fine movements needed to articulate a tongue twister or pick a raspberry without crushing it. *Different types of muscle fibers are mixed in proportions appropriate to the common usages of each muscle.*

Skeletal muscle comes in two basic varieties:

- **Slow-twitch** fibers generate forces slowly and maintain these forces for a long time.
- **Fast-twitch** fibers generate large forces rapidly but tire quickly.

Slow-twitch fibers require oxygen to function and are supplied amply with capillaries carrying oxygenated blood. Slow-twitch fibers contain myoglobin,

DARK AND LIGHT CHICKEN MEAT STEMS FROM THE GREATER VASCULARIZATION IN SLOW-TWITCH MUSCLE THAN IN FAST-TWITCH MUSCLE.

The breast muscles of chickens are composed primarily of fast-twitch muscle, whereas the leg muscles are composed primarily of slow-twitch muscle. Thus, meat, which is simply skeletal muscle, from the breast is paler than meat from the leg. In general, most flying birds have exclusively, or nearly exclusively, slow-twitch muscles. Slow-twitch muscles, which maintain contractions for a lot longer than do fast-twitch muscles, are used during long-duration flights. Chickens, of course, do not fly much.

a heme-containing protein that transports oxygen and gives the fibers their red appearance, to the mitochondria that support aerobic metabolism. As slow fibers depend on diffusion of oxygen from nearby capillaries, there is an upper limit to their size. Fast-twitch fibers differ from slow-twitch fibers in almost all respects. Fast-twitch fibers function either partially or entirely by anaerobic glycolysis. Fast-twitch fibers that can function both aerobically and anaerobically using glycolysis are called **oxidative glycolytic** fast-twitch fibers, whereas fast-twitch fibers that function exclusively by anaerobic glycolysis are called **glycolytic** fast-twitch fibers. Muscle fibers that rely progressively more upon glycolysis are progressively paler in color and less vascularized (see Box 21-1). As fast fibers depend either in part or wholly on glycogen stores that are distributed throughout the cell, fast fibers *can* be, but are not always, large in size. The force exerted by a contracted muscle fiber depends on its cross-sectional area. Therefore, the maximal contractile force is greater in the larger fast-twitch fibers than it is in slow fibers.

Slow- and fast-twitch muscle fibers differ in two main *contractile* features:

- Speed of force generation
- Endurance or ability to maintain force over time

The difference in contractile speed stems from variations in contractile molecules and their regulation by calcium. Fast-twitch muscle fibers contract two to three times more rapidly than do slow-twitch muscle fibers. Yet, slow fibers can contract for longer periods of time because the oxygen keeps coming, but fast fibers can only use glycogen stores for a limited amount of time before the available glycogen is depleted. After glycogen depletion, fast glycolytic fibers cannot contract again until the glycogen stores are replenished, a process that can take hours. Fast oxidative glycolytic fibers, on the other hand, function aerobically after their glycogen supply is exhausted, so that these fibers can operate for a longer time than can fast glycolytic fibers.

In sum, we recognize three types of skeletal muscle fibers (see Table 21-1):

- Oxidative slow-twitch muscle fibers generate forces slowly and are highly resistant to fatigue. They are active during small, steady contractions that last for hours.
- Oxidative glycolytic fast-twitch muscle fibers generate forces at an intermediate speed and fatigue within 5–30 minutes.
- Glycolytic fast-twitch muscle fibers generate forces very rapidly. Yet, they cannot sustain contractions for more than a few minutes, and after exhaustion may require hours to recover.

In muscles that are active for long periods such as those that maintain posture, close off the urethra during hours of urine storage, or grip a briefcase while walking to work, slow-twitch fibers, which can provide long-lasting, tonic contractions, predominate. One can think of cardiac muscle, which can only operate

TABLE 21-1. THE CHARACTERISTICS OF THE THREE TYPES OF MUSCLE FIBERS ARE SUMMARIZED

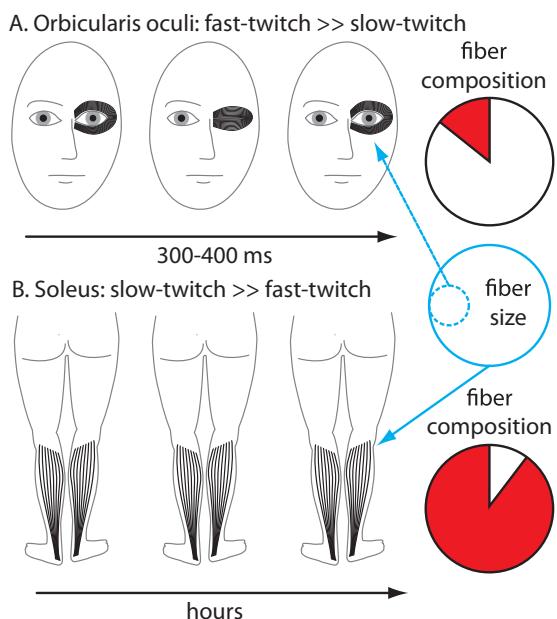
CHARACTERISTIC	SLOW-TWITCH FIBERS	OXIDATIVE GLYCOLYTIC FAST-TWITCH FIBERS	GLYCOLYTIC FAST-TWITCH FIBERS
Energy source	Aerobic only	Aerobic and anaerobic glycolysis	Anaerobic glycolysis only
Speed of contraction	Slow	Intermediate	Fast
Maximal duration of continuous activation	Hours	≤30 minutes	≤5 minutes
Upper size limit	Small	Intermediate	Large
Upper limit for twitch tension	Low	Intermediate	High

The upper size limit refers to the largest physical dimensions of a fiber of each type. Slow-twitch fibers depend on oxygen for their operation and thus have the smallest upper limit in fiber diameter of the three types. The fiber size is the major determinant of the maximal amount of tension produced by a twitch. Therefore, the upper limit of twitch tension largely reflects the upper limit on fiber size. Note that there are muscle fibers of each type that are smaller in diameter and produce less tension than the upper limits possible.

aerobically and does so for a lifetime (by definition), as the epitome of a slow-twitch muscle. In contrast, muscles with a large proportion of fast-twitch fibers support ballistic movements such as jumping and blinking. *The proportions of slow-, oxidative glycolytic fast-, and glycolytic fast-twitch muscle fibers in a muscle match the functions of that muscle* (Fig. 21-1). For instance, the soleus muscle is an ankle extensor that is nearly maximally contracted during standing and maintains nearly the same tension during locomotion. Thus, the soleus, like other postural extensors, is tonically contracted for long periods of time as it opposes the force of gravity, and contains predominantly slow-twitch fibers (see Box 21-2). The small force and long endurance provided by slow-twitch fibers exactly match the requirements for optimal soleus

Figure 21-1. A: One major use of the orbicularis oculi is for blinking, a ballistic movement, that is initiated and completed in less than a half second. The orbicularis oculi consists mostly of fast-twitch fibers (white area in pie graph) and has only a small proportion of slow-twitch fibers (red area in pie graph). B: The soleus muscle flexes the ankle, keeping the body from falling backward. The soleus is the primary muscle employed in standing and can continue to contract for hours. Befitting its long duration use, the soleus muscle contains mostly slow-twitch fibers. The average fiber size of orbicularis oculi muscle fibers is far smaller (dashed blue circle) than the average fiber size of soleus muscle fibers (blue circle).

Data obtained from Johnson, M.A., Polgar, J., Weightman, D., and Appleton, D. Data on the distribution of fibre types in thirty-six human muscles An autopsy study. *J Neurol Sci* 18: 111-29, 1973; and Polgar, J., Johnson, M.A., Weightman, D., and Appleton, D. Data on fibre size types in thirty-six human muscles An autopsy study. *J Neurol Sci* 19: 307-28, 1973.



Box 21-2

TONIC AND PHASIC ARE TERMS THAT REFER TO PROLONGED AND TRANSIENT TIME COURSES, RESPECTIVELY.

Tonic refers to a process that is ongoing over a relatively long period of time, whereas *phasic* refers to a burst of activity that starts and ends within a short period of time. For example, the paraspinal muscles in the back keep one sitting or standing for as long as they are tonically active, whereas the paraspinal muscles are only phasically active as one rises from picking something off the ground.

Box 21-3

MOTONEURONS AND MOTOR CORTICAL CELLS EACH HAVE UNIQUE AND DISTINCT PROPERTIES.

Recall from Chapter 1 that the clinical literature often utilizes the term **upper motor neurons** to refer to cells in motor cortex and refers to motoneurons that actually contact skeletal muscles as **lower motor neurons**. As explained fully in Box 1-10, this terminology disregards the unique character and function of both motoneurons and cells in motor cortex. The terms are not used in this book.

function. In contrast, the orbicularis oculi is active almost exclusively during eye blinks—rapidly-initiated, **phasic** or short-lived, ballistic movements—and appropriately contains mostly fast-twitch muscle fibers.

The size of muscle fibers in any given muscle is appropriate to the force requirements of movements made by that muscle and does *not* only depend on fiber type. For example, fast-twitch fibers in the orbicularis oculi are used for eye blinks, whereas limb and axial muscles operate on much heavier objects, including the body itself. In addition to the orbicularis oculi having fewer fibers than a limb muscle such as the biceps, the average diameter of fast-twitch fibers in the orbicularis oculi is less than half that of fast-twitch fibers in limb and axial musculature (Fig. 21-1).

Most muscles are “mixed,” containing both slow- and fast-twitch fibers, and therefore can participate in both tonic and phasic activities. For example, the gastrocnemius (calf muscle) is minimally contracted during standing, but activated increasingly during walking, jogging, running, and sprinting. Appropriately, the gastrocnemius contains both slow- and fast-twitch fibers with more fast oxidative glycolytic than fast glycolytic fibers, allowing for long-lasting engagement in locomotion.

THE MOTOR UNIT IS THE SMALLEST DIVISION OF MOVEMENT

As introduced in Chapter 1, the motoneuron is the only conduit from the central nervous system to skeletal muscle (see Box 21-3). Each motoneuron innervates a number of muscle fibers, whereas any single muscle fiber is innervated by only one motoneuron at only one synaptic site in the adult. *Thus, the smallest functional unit of the motor system is one motoneuron and the muscle fibers that it innervates.* This is the **motor unit**. When a motoneuron fires, all muscle fibers innervated by that motoneuron contract. In the absence of input from a motoneuron, none of the innervated muscle fibers contract. Thus, *the motor unit is the quantum of the motor system, the smallest operating unit that can be engaged.*

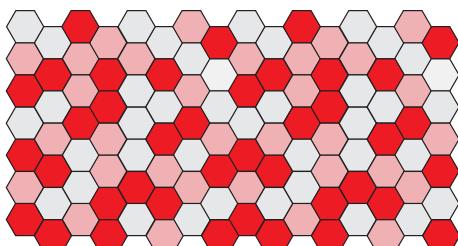
Muscles used for finely graded movements contain motor units with fewer fibers than do muscles used for more forceful and less carefully controlled movements. Some motoneurons innervating muscles that produce coarse movements (e.g., calf and quadriceps muscles) innervate hundreds or thousands of muscle fibers in the human. In contrast, motoneurons innervating muscles that produce finely controlled movements (e.g., hand muscles) innervate far fewer muscle fibers, typically less than 100, whereas motoneurons innervating muscles that allow for extremely precise movements, such as extraocular muscles, innervate fewer than 10 muscle fibers (see Chapter 26).

All muscle fibers innervated by any one motoneuron are of one type—either slow-twitch, oxidative glycolytic fast-twitch, or glycolytic fast-twitch (Fig. 21-2). Reflecting the one-to-one relationship between motor units and fiber type

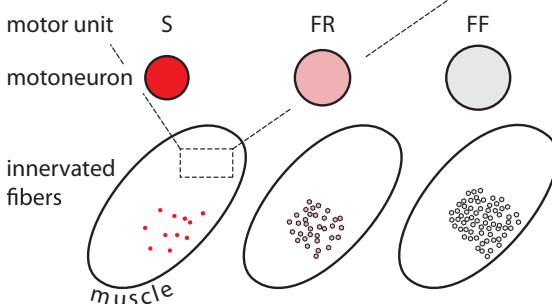
Figure 21-2. A: In mixed muscles, different fiber types are interspersed rather than segregated in one portion of the muscle. Consequently, injury to one part of a muscle does *not* preferentially affect one muscle fiber type over another. This cartoon diagrams the muscle fibers (hexagons) in a cross-section through a mixed muscle such as the gastrocnemius. Slow-twitch (red), oxidative glycolytic fast-twitch (pink), and glycolytic fast-twitch (light gray) muscle fibers are interspersed in an apparently random fashion. B: Motor units consist of a motoneuron and the muscle fibers that that single motoneuron innervates. Motor units are the quanta of the motor system. S motor units innervate slow-twitch muscle fibers. Fast fatigue-resistant (FR) motor units innervate oxidative glycolytic fast-twitch muscle fibers. Fast fatigable (FF) motor units innervate glycolytic fast-twitch muscle fibers. The muscle fibers of a single motor unit, of any type, are scattered through a large portion of a muscle and are rarely contiguous.

Modified from Burke, R.E., and Tsairis, P. Anatomy and innervation ratios in motor units of cat gastrocnemius. *J Physiol* 234(3): 749-65, 1973 with permission of the publisher, Wiley.

A. Mixed muscle



B. Motor units



innervated, there are three types of motor units. **Slow** or **S** motor units innervate slow-twitch muscle fibers. Activation of S units produces slowly building muscle tension that can be sustained for hours. **Fast fatigue-resistant** or **FR** motor units innervate oxidative glycolytic fast-twitch muscle fibers. Activity in FR units produces rapid increases in muscle fibers that use both aerobic and anaerobic metabolism to sustain contractions for tens of minutes. The final type of motor unit is the **fast fatigable** or **FF** motor unit. Activity in FF units leads to very rapid increases in muscle tension. However the glycolytic fast-twitch fibers excited by FF units can only maintain a contraction for a few minutes at most. In this way, *the characteristics of each motor unit type reflect the properties of the innervated muscle fibers*.

THE MAXIMAL FORCE PRODUCED BY A MOTOR UNIT DEPENDS PRIMARILY ON THE NUMBER OF MUSCLE FIBERS INNERVATED

The maximal force produced by a motor unit depends mainly on the number of muscle fibers innervated or the **innervation ratio** (see Box 21-4). In general, the innervation ratio is lowest in S units, greatest in FF units, and intermediate in FR units. Thus, each S motor unit innervates a small number of muscle fibers and produces a small total force, whereas each FF motor unit innervates a large number of muscle fibers and produces a large force.

Because of the small force exerted by each S motor unit, a large number of S motor units make a disproportionately small contribution to the maximal contractile

**THE FORCE
PRODUCED BY
DIFFERENT MOTOR
UNITS DEPENDS
PRIMARILY ON THE
INNERVATION RATIO
AND ON MUSCLE
FIBER DIAMETER.**

Beyond the number of muscle fibers innervated by a motoneuron, the *innervation ratio*, two additional factors make small contributions to the difference in forces produced by each motor unit type. First, greater forces are produced by larger diameter muscle fibers. Since muscle fibers with glycolytic capacity can be larger than those that depend solely upon aerobic function, large muscles like the quadriceps have larger-diameter fast-twitch fibers than slow-twitch fibers. However, this factor does not contribute in small muscles, in which the upper limit of muscle fiber diameter is well within the range of slow fibers limited to oxidative function. The second additional factor is that the force output per unit area may be *slightly* greater in fast than slow fibers.

force of a muscle (Fig. 21-3). Similarly, because of the large force exerted by each FF motor unit, FF motor units contribute disproportionately more than their numbers to the maximal contractile force of a muscle. In other words, S motor units contribute much less and FF units more to the total force of a muscle than would be predicted by their representation within the motoneuron population.

The profiles of different motor unit types allow us to predict the consequences of injury to selected motor unit populations. *Loss of just a few FF or FR motor units will drastically compromise maximal muscle contraction.* In contrast, many S motor units must be injured before a serious reduction in contractile force would be observed. However, *the loss of even a few S motor units may negatively impact the endurance capacity of a muscle without significantly weakening it.*

MOTONEURON FIRING RATE AND PATTERN ARE CRITICAL TO SETTING MUSCLE TENSION

Muscle fibers do not contract without motoneuronal input. The strength of the contraction determines the muscle tension produced. The relationship between motoneuronal firing and muscle tension depends on two factors:

- The immediate (tens of milliseconds) history of activity in the innervating motoneuron
- The “warm-up” (minutes) history of the innervating motoneuron

The immediate influence of motoneuron firing on muscle fiber tension is fairly simple: the more frequently a motoneuron fires, the greater the muscle tension that develops. This positive correlation between motoneuron firing rate and muscle tension operates until the maximal tension possible is produced. The effect of warm-up is to multiply the effect of each action potential. Thus, a warmed-up

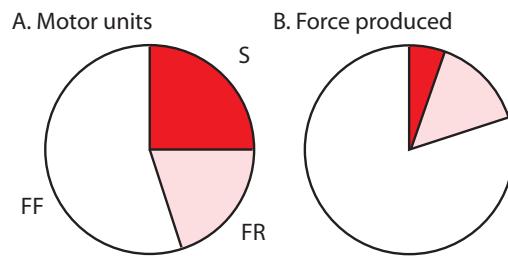
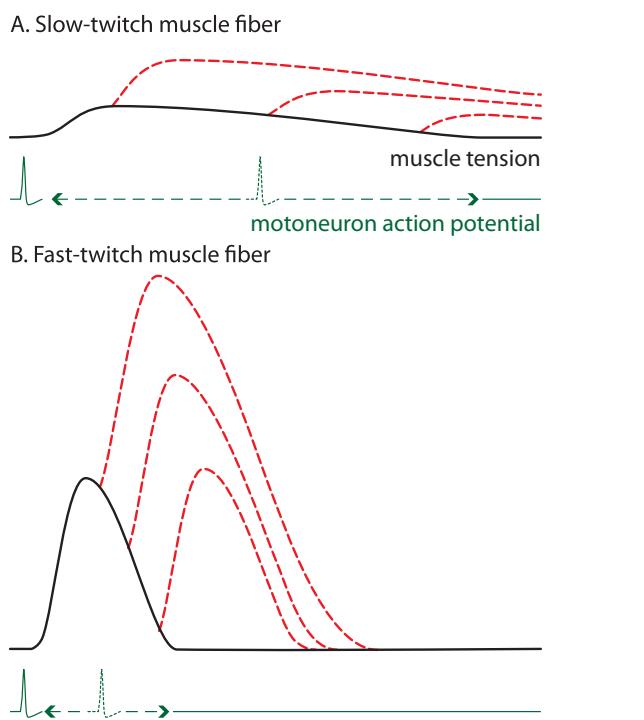


Figure 21-3. In the case of the gastrocnemius muscle, a typical mixed-limb muscle, S motor units (red) make up 25% of the total motor units (A) but contribute less than 5% of the force (B). In contrast, FF motor units (white) make up 55% of the motoneuron pool (A) and contribute 80% of the force (B). The number and contribution of FR motor units (pink) are intermediate.

Figure 21-4. Action potentials are short (~1 ms), but produce long-lasting changes in muscle tension. **A:** A single action potential (lower trace in green) produces a slowly developing, long-lasting, small increase in the tension of a slow-twitch motor unit (black). A second action potential (dotted green) following the initial action potential within about 100 ms (period encompassed by green arrows) produces an additive effect on muscle tension (dashed red traces) but this effect decreases at increasing intervals. **B:** A single action potential (lower trace in green) produces a rapidly developing and large magnitude, but short-lived increase in the tension of a glycolytic fast-twitch muscle fiber (black). A second action potential (dotted green) must follow the initial action potential within about 40 ms (period encompassed by green arrows) to produce an additive effect on muscle tension (dashed red traces), an effect that, as in the case with a slow-twitch muscle fiber, decreases at longer intervals.

Modified from Burke, R.E., Rudomin, P., and Zajac, F.E., 3rd. The effect of activation history on tension production by individual muscle units. *Brain Res* 109: 515–529, 1976 with permission of the publisher, Elsevier.



muscle produces greater tension in response to a single action potential than does a cold muscle.

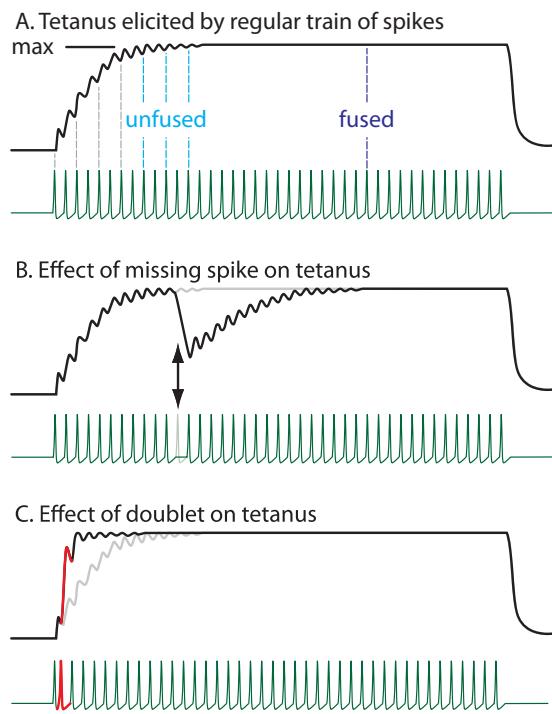
To understand how these processes work together, we first look at the muscle tension produced by a single action potential. The increase in muscle tension persists for a much longer time than does the motoneuron action potential (Fig. 21-4). Slow-twitch fibers produce the longest-lasting increase in tension (up to 100 ms), fast glycolytic fibers the shortest-lasting increase (as short as 3 ms but typically closer to 20–30 ms), and fast oxidative glycolytic fibers produce tension of intermediate duration (30–50 ms). Because of the long-lasting muscle twitches, a second action potential occurring within the period of elevated muscle tension evokes a summing muscle tension.

When a train of action potentials occurs in a motoneuron, the forces generated in the innervated muscle fibers resulting from each successive action potential sum until contraction reaches a maximal level, representative of the maximal contraction possible for that muscle (Fig. 21-5A). At moderate rates of motoneuron discharge, the individual contractions due to each action potential are still distinguishable in a recording of muscle force; this is termed an **unfused tetanus**. At higher rates, however, the individual contractions evoked by single action potentials are no longer distinguishable. Instead, the tension generated during a **fused tetanus** reaches and maintains a smooth plateau level. *Fused tetanus represents the maximal force that a muscle can generate; increasing the motoneuron firing rate beyond that which produces fused tetanus produces no additional force.*

If one action potential is missed from a regular train of action potentials, the result is a disproportionately large drop in muscle tension (Fig. 21-5B). Conversely, if an extra action potential sneaks into an otherwise regular train of action potentials,

Figure 21-5. A: A train of regularly timed action potentials in a motoneuron produces regularly timed and summing increases in muscle tension. When the maximal muscle tension (*max*) is reached, the effect of each action potential is still apparent. This is termed *unfused tetanus*. Fused tetanus occurs when action potentials have no additional effect on muscle tension. B: Omission of a single action potential (*pale green*) greatly decreases muscle tension and prolongs the latency to fused tetanus. C: Two action potentials occurring at a short interval are termed a *doublet*. The effect of a doublet (*red*) is a large increase in muscle tension (*red*) and an augmentation of the effect of each subsequent action potential. As a result, both unfused and fused tetanus occur at earlier latencies. In B and C, the original tetanus shown in A is drawn in gray.

Modified from Burke, R.E., Rudomin, P., and Zajac, F.E., 3rd. The effect of activation history on tension production by individual muscle units. *Brain Res* 109: 515–529, 1976, with permission of the publisher, Elsevier.



muscle tension is abruptly, and inordinately, increased (Fig. 21-5C). The sensitivity of muscle tension to the pattern of action potentials is important as alterations to the timing of action potentials, such as occur in demyelinating diseases, profoundly alter the profile of muscle contraction.

Just as the occurrence of an action potential alone or within a train influences the magnitude of the resulting muscle tension, past usage of the muscle also influences the tension evoked by a single spike. *Excitation of a previously tetanized muscle fiber results in a far larger output than does excitation of a previously inactive fiber.* Although full tetanus facilitates muscle tension per action potential optimally, even a few isolated twitches augment the ensuing level of muscle tension produced by a single action potential. In sum, “warming-up” multiplies the muscle tension produced by every subsequent action potential occurring over the course of the next several minutes. Maximal warm-up, meaning reaching tetanus, maximally facilitates the effect of subsequent action potentials.

ORDERLY RECRUITMENT PRODUCES MOVEMENTS THAT INCREASE IN FORCE SMOOTHLY WITH MINIMAL MUSCLE FATIGUE

Motoneurons belonging to the three types of motor units differ in physiological properties, most importantly input resistance. The input resistance of S motoneurons is greatest and that of FF motoneurons lowest (see Table 21-2). Recall from Chapter 4 that, because of Ohm’s Law ($V = I \cdot R$), a cell

TABLE 21-2. THE CHARACTERISTICS OF THE THREE CATEGORIES OF MOTOR UNITS ARE SUMMARIZED

PHYSIOLOGICAL PROPERTY	S MOTOR UNITS	FR MOTOR UNITS	FF MOTOR UNITS
Type of muscle fiber	Slow-twitch fibers	Oxidative glycolytic fast-twitch fibers	Glycolytic fast-twitch fibers
Rise time	Slow (50–100 ms)	Intermediate (30–50 ms)	Fast (3–30 ms)
Maximal duration of continuous activation	Hours	≤30 minutes	≤5 minutes
Innervation ratio	Lowest	Low	Highest
Upper limit for tetanic tension	Low	Intermediate	High
Input resistance	High	Intermediate	Low
Current threshold for activation	Low	Intermediate	High

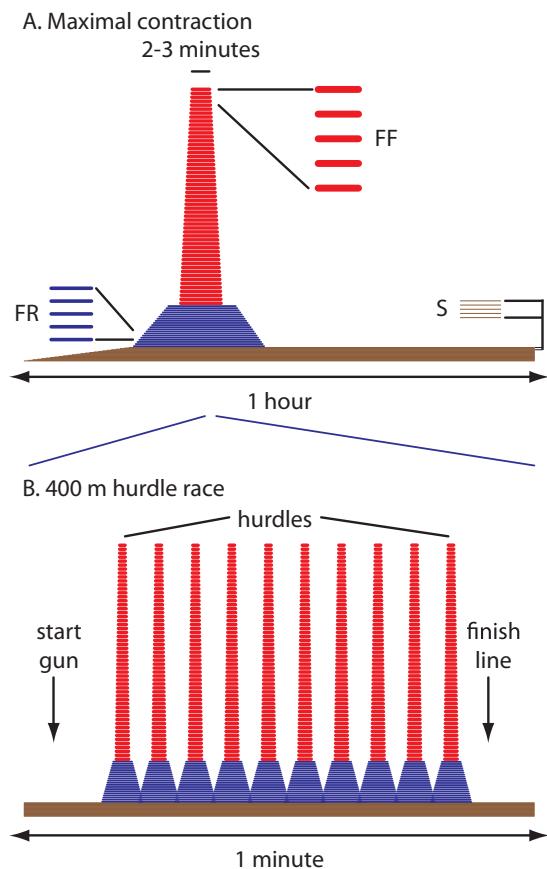
The kinetic properties of motor unit types (*red text*) reflect the properties of the muscle fiber types innervated. The innervation ratio, input resistance, and current threshold of activation are all characteristics of the motoneuron. The upper limit for tetanic tension produced is primarily a consequence of the innervation ratio but is also influenced by fiber type.

with a high input resistance requires a lower synaptic current to reach the action potential threshold than does a cell with a lower input resistance. As a result, cells provided with the *same synaptic current* are activated in the order of decreasing input resistance. This means that S motoneurons are activated before FR motoneurons, which are activated before FF motoneurons, so that *if provided with a common input, motor units are activated in a sequence of increasing force*. S motor units are activated first, FR units second, and FF units last (Fig. 21-6A). The sequential engagement of S, FR and FF motor units is termed **orderly recruitment**.

Orderly recruitment matches output to demand. To understand this concept, consider three activities: standing, walking, and jumping. Of the three activities, standing requires the smallest force but lasts the longest amount of time. The attributes of S motor units match the low force, long endurance requirements of postural muscles. Walking depends on greater muscular forces, but these forces are needed for less time than in the case of standing. Thus, FR motor units, working with still-engaged S motor units, are suited to support walking. Finally, jumping requires a large contractile force for a very short time, needs met by adding activation of FF motor units to the already-activated S and FR units. Even when not exercising, we continually engage S motor units to exert small forces that maintain our body position, whether we are prone, sitting, or standing. Only upon this background do we start to move about, engaging FR units to walk or jog. Similarly, we typically run before leaping, a brief action that requires activation of FF units in the context of still-contracted S and FR units (see Box 21-5).

The sequential engagement of motor units in the S→FR→FF order combines with a progressive increase in the number of innervated muscle fibers in each successively activated motor unit. Thus, the first S motor units activated innervate fewer muscle fibers than do subsequently activated S motor units and so on. *The progressive*

Figure 21-6. A: When a person is asked to maximally contract a muscle, S motor units (brown) are recruited first, followed by FR motor units (blue), and FF motor units (red) are recruited last. Motor units fatigue in the reverse order of their recruitment. Thus, in a person trying to hold a maximal muscle contraction, the FF motor units drop out first, after only a few minutes. FR motor units drop out within 15–30 minutes. S motor units are highly resistant to fatigue and can maintain a contraction for hours. The insets show the relative force produced by five motor units of each type. S motor units produce less force than FR motor units, which in turn produce less force than FF motor units. B: The recruitment of motor units in a muscle used primarily for jumping, such as a hip flexor, is diagrammed over the course of a 400 m hurdle race. An elite hurdler runs a 400 m hurdle race in just under a minute. For each hurdle there is a brief, a second or two, and explosive increase in muscle tension in the hurdling muscles. Note that the recruitment pattern for muscles primarily involved in running would look quite different.



increase in force produced by successively activated motor units ensures that muscle tension increases smoothly, devoid of sudden jerks or failures. De-recruitment, relaxing a muscle, happens in the reverse order from recruitment. So, FF motor units “drop out” first followed by FR motor units, whereas S motor units remain contracted for hours. Minimally invasive **electromyography** allows a glimpse into the recruitment and drop out of motor units in accessible human muscles and is used to diagnose myopathies and motoneuron diseases (see Box 21-6).

Advantages derive from the sequential activation of S, FR, and FF motor units and the reverse order drop-out of motor unit types. First, *failure due to fatigue is minimized* because S motor units are activated first and for the longest time during long-lasting activities. Second, *the increment of force produced by the recruitment of each additional motor unit is proportional to the existing force in the muscle*. This is a sort of motor equivalent to Weber’s sensory law (see Chapter 15) that enables a person to both exert finely graded pressure on a foot pedal and kick a ball. Thus, small increments of force add upon a background of low force to enable finely controlled movements, whereas large increments of force add upon a background of great force for ballistic movements.

Orderly recruitment depends on a common input to all of the motor units innervating a muscle. However, not all inputs are distributed evenly to motoneurons of all three types. For example, cutaneous nociceptors excite FF and FR motor units but not S motor units. This advantageous organization allows a noxious input to elicit a rapid

WEIGHT-BEARING EXERCISE ALTERS MOTOR UNIT RECRUITMENT.

S motor units are used daily but FF and FR motor units are used much less often. In sedentary individuals, engagement of FF motor units is rare, particularly in muscles that are not used in everyday activities. When asked to make a maximal contraction, sedentary adults produce up to 95% of the maximal force that their muscle can produce. The unactivated fibers, those with the highest threshold for activation, are FF motor units. An *immediate effect of exercise*, an effect that is sustained for weeks after a single workout of strength training, is the facilitation of FF motor unit recruitment. *This enables the voluntary contraction of more FF motor units and the capacity to reach 100% of a muscle's contractile strength.*

A pair of action potentials that occurs in rapid succession, termed a **doublet**, evokes a very large and abrupt increase in muscle force (Fig. 21-5C). Doublets increase the force of muscle contraction more than would the same pair of action potentials separated by a longer interval. Exercise may increase the incidence of doublets in motoneurons. It is also

possible that strength training increases the synchrony of motor unit recruitment, so that more motor units are recruited together at one time.

In addition to the effect of exercise on recruitment of the FF motor units with the highest thresholds, the firing rate of motor units is elevated for some weeks after individuals start an exercise program. However, after 6 weeks or so of training, the firing rate decreases back to pretraining levels. This late decrease appears as muscle mass, and therefore strength, increases. Exercise of different sorts causes specific changes in the muscle itself. Endurance training markedly increases the density of mitochondria and thus the aerobic capacity of muscle fibers. Consequently, muscles in trained individuals can be active for longer periods without fatiguing. Weight training primarily increases muscle mass—increasing the diameter of muscle fibers—and altering certain contractile properties of muscle. Remember that the force produced by a muscle fiber is proportional to its diameter. So, as one “builds” muscles, the contractile force of each component motor unit increases.

and ballistic movement without a slow buildup in muscle tension. Beyond cutaneous afferents, few additional inputs that may utilize this “shortcut” to FF and FR motor units have been identified.

In sum, the total force or tension generated by a muscle depends on the number, type, and size of the motor units recruited and on the number and frequency of action potentials fired by the recruited motoneurons in the immediate and recent past. Muscles dominated by slow-twitch fibers predominantly utilize action potential rate as the determinant of muscle force, whereas mixed muscles predominantly use recruitment of additional motor units.

Consider a hurdler on race day. The hurdler warms up—jogging, running, and jumping a hurdle or two—and by so doing tetanizes the same muscles that will be engaged during the race. Even this brief muscle activation greatly facilitates the amount of force that will be produced by the same muscle fibers during the race. A number of S motor units firing at moderate frequencies support the hurdler in the moments prior to the race’s start. As the hurdler enters the starting blocks and gets set, the firing rate of the active motor units, still mostly S units, increases. When the starting gun goes off, these activated S motor units reach full tetanus, exerting maximal force, and will remain so activated throughout the race. FR and FF motor units innervating muscles critical to running are recruited and fire at peak, or near peak, frequencies when the hurdler explodes out of the starting blocks. In the sprint to the

ELECTROMYOGRAPHY IS A MINIMALLY INVASIVE CLINICAL TEST THAT CAN MEASURE MOTOR UNIT FUNCTION.

The motor unit is one of the most accessible physiological processes in the nervous system. Thin needles placed in muscles allow physicians to make **electromyographic** or **EMG** recordings of muscle activity. These EMG tests help distinguish between problems in muscle, termed **myopathies**, **motoneuron diseases**, and dysfunction of higher motor centers, such as can occur with multiple sclerosis or stroke.

Electromyography, typically called *EMG testing*, involves inserting a metal recording electrode through the skin into the belly of a muscle. The electrode records extracellular action potentials in surrounding muscle fibers. The nearer the electrode is to the muscle fiber, the larger the recorded action potential. Since the muscle fibers innervated by each motoneuron are scattered throughout the muscle, activity in any motor unit is likely to include at least some fibers within the range of the recording electrodes. However, remember that either all or none of the fibers in a motor unit contract at one time. Therefore, activity in each motor unit will cause a particular size and shape of voltage deflection, so that the waveform serves as that motor unit's signature.

Let us begin by considering how EMG testing **should** appear in a healthy individual. At rest, there should be no activity, meaning no action potentials, in a muscle (Fig. 21-7A). As the patient voluntarily contracts the muscle being studied, one or a few S motor units are recruited; this appears as repeated action potentials (Fig. 21-7B). Once a motor unit fires at about 10 Hz, another motor unit is recruited. When the second one also fires at a rate of at least 10 Hz, additional motor units are recruited, and so on. With increasing strength of voluntary contraction, more and more motor units become active. Eventually, when a person is voluntarily contracting at maximal strength, many motor units are all firing together, giving rise to a noisy and large-amplitude recording in which single motor units are no longer discernible (Fig. 21-7C).

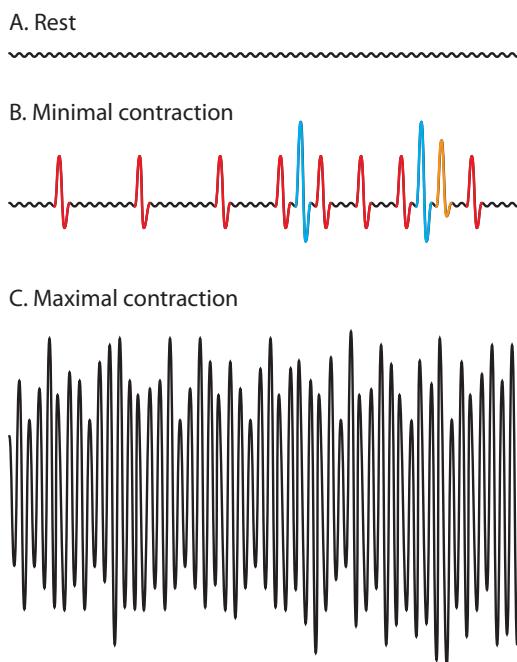
Now, let us consider what to expect from patients with a primary muscle disease such as **polymyositis**. Since the muscle itself is the target and becomes weak, the potentials recorded from muscle

are small in amplitude and are relatively few, even at maximal contraction. In a patient with a motoneuron disease such as **spinal poliomyelitis**, colloquially known as polio, motoneurons die, killed by the polio virus, which results in muscle weakness or paralysis. As more and more motoneurons die, there are fewer motor units available. So, when the first motor unit reaches 10 Hz, another motor unit *may not be available*. If another motor unit is not available—because the motoneuron has died—the first motor unit fires faster, without a second motor unit being recruited. This is termed **reduced recruitment**. Both motoneurons and muscle fibers undergo changes when the innervation from motoneuron to muscle fibers is disrupted. Muscle fibers that lose their innervation—are **denervated**—eventually waste away or **atrophy**. In the presence of denervated muscle fibers, motoneuron axons sprout new endings that innervate denervated muscle fibers. So, the remaining motoneurons innervate extra muscle fibers, resulting in motor unit potentials that are larger than normal.

Fasciculations are visible twitches that result from activation of an entire motor unit. In patients with motoneuron disease, fasciculations can be quite large as the surviving motoneurons innervate extra muscle fibers, as explained above. Before a large portion of you panics that you have motoneuron disease—as much as 50%–60% of the population experiences fasciculations—and *most fasciculations are benign*. Further, people with benign fasciculations are not more likely than others to develop motoneuron disease.

In contrast to fasciculations, **fibrillations** represent single action potentials that are not visible and thus represent an **electrical sign**—a sign only seen with EMG recording methods—rather than an observable symptom. Fibrillations arise in denervated muscle, which has supersensitive acetylcholine receptors that respond to acetylcholine circulating in the blood. Note that in contrast to fasciculations, visible twitches resulting from activation of an entire motor unit, fibrillations involve the contraction of lone muscle fibers rather than all of the muscle fibers in a motor unit. Fibrillations are the only type of muscle contraction involving a muscle division smaller than the motor unit.

Figure 21-7. Idealized records from electromyographic (EMG) testing at rest (A) and with increasing voluntary contraction (B–C) in a healthy individual. Each motor unit is characterized by a particular waveform or electrical signature. A: At rest, no motor units are active. B: During minimal contraction, a few distinct motor units occur. In this trace, there are three units active. The red unit is most active, and with time, the blue and orange units are recruited. C: During maximal contractions, individual units are no longer detectable. The activity during maximal contractions is continuous and larger in amplitude than the activity during minimal contractions. The large amplitude of EMG recordings during maximal contractions reflects (1) the recruitment of glycolytic fast-twitch fibers, which have larger amplitude waveforms; and (2) the addition of waveforms from simultaneously active motor units.



first hurdle, the FR and FF motor units needed for running are recruited by FR and FF motoneurons firing at near maximal frequency for the entirety of the race. At each hurdle, FR and FF motor units innervating muscles needed for jumping are recruited (Fig. 21-6B). Critically, by ensuring that each increase in contractile force is proportional to the existing level of muscle activation, orderly recruitment prevents both an inappropriately large and therefore jerky contraction during standing and an inappropriately small, and therefore inconsequential and potentially disastrous, contraction during hurdling.



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CHAPTER 22

REFLEXES AND GAIT

MOTONEURONS AND LOCAL INTERNEURONS PRODUCE REFLEXIVE AND SEMIAUTOMATIC MOVEMENTS

Motor circuits within the spinal cord and brainstem support reflexive movements and quick feedback adjustments to changed circumstances. Reflexes allow a person to recover from stumbling over a tree root or open a door that is heavier than expected. Central pattern generator circuits produce semiautomatic movements such as walking, running, and chewing. These are the topics covered in this chapter.

THE STRETCH REFLEX CORRECTS FOR UNEXPECTED LOADS

Thus far, we have described how action potentials in motoneurons produce contractions (see Box 22-1) in selected muscle fibers. Now, what happens when something unexpected occurs? Consider walking along and encountering a tree root in the path. As your foot hits the immovable root, a reflex to recover from stumbling takes over, preventing a fall. You do not have to plan this motion, prepare for it, think about it, or practice it daily. Instead, you recover from a stumble *reflexively*, without practice or forethought. The automatic engagement of the stumbling corrective reflex is rooted in spinal circuits and thus happens very quickly, within 10–50 ms of encountering the obstacle, allowing people to recover from stumbles before actually falling to the ground.

The spinal cord and brainstem mediate a number of stereotyped, behavioral responses called *reflexes*. The stumbling corrective reflex is a highly intricate reflex; at the opposite end of the complexity spectrum, the *stretch reflex*, also known as the *myotactic reflex*, is the simplest vertebrate reflex. The precipitating stimulus for the stretch reflex is a stretch, also termed a *load*, an added and unexpected force that stretches a muscle. The stretch reflex involves only one synapse within the central nervous system and therefore is termed *monosynaptic*. In counting synapses involved in a circuit, we count only those between two neurons; the synapse from motoneuron to muscle is not counted. *The only monosynaptic reflex in the human is*

Box 22-1

MUSCLE CONTRACTIONS CAN BE ACCOMPANIED BY MUSCLE SHORTENING OR LENGTHENING OR BY NO CHANGE IN MUSCLE LENGTH.

Muscle shortening often, but not always, accompanies muscle **contraction**. In **isometric** muscle contractions, muscle does not change length while exerting force. For example, the biceps exerts force to hold a baby while maintaining a constant length. Perhaps less widely appreciated are muscle contractions associated with muscle-lengthening, termed **eccentric**. Eccentric muscle contractions occur commonly. For example to lift a baby in the air, the biceps contracts but also lengthens. When the load on a muscle exceeds the muscle's maximal contractile force, all

contractions are eccentric. Thus, you can carry (isometric) and put down (eccentric) a weight that you may not be able to lift (muscle-shortening). Interestingly, eccentric exercise strengthens muscles more effectively than isometric or muscle-shortening exercises. Eccentric contraction also creates tiny muscle tears. These tears appear to be largely responsible for the muscle soreness that occurs the day after a new or particularly strenuous workout. After a few days, these small tears and the associated soreness resolve.

Box 22-2

DURING ACTIVE MOVEMENTS, ANTAGONIST MUSCLES ARE STRETCHED WHEN AGONIST MUSCLES SHORTEN.

Stretches arise when a load extends a muscle. For example, when coming down a staircase, the body (a load) results in a stretch of the ankle extensor muscles of the leading leg. At landing, as the body accelerates earthward and forward, the resulting stretch elicits a reflexive excitation of the homonymous muscle, thereby opposing the original stretch and contributing to an upright landing. Minute stretches engage Ia afferents all the time, permitting us to maintain our posture on a moving train, carry a squirming child, and catch a softball.

What about the type of stretching that one does before and after exercising? These athletic stretches have a number of effects. Within the muscle, stretches break actin-myosin bonds that form in inactive muscle and stretch titin, increasing muscle elasticity. In active stretches, such as a lunging stretch of the gastrocnemius muscles, that require activation of antagonist muscle, there is the added effect of potentiating the antagonist muscle.

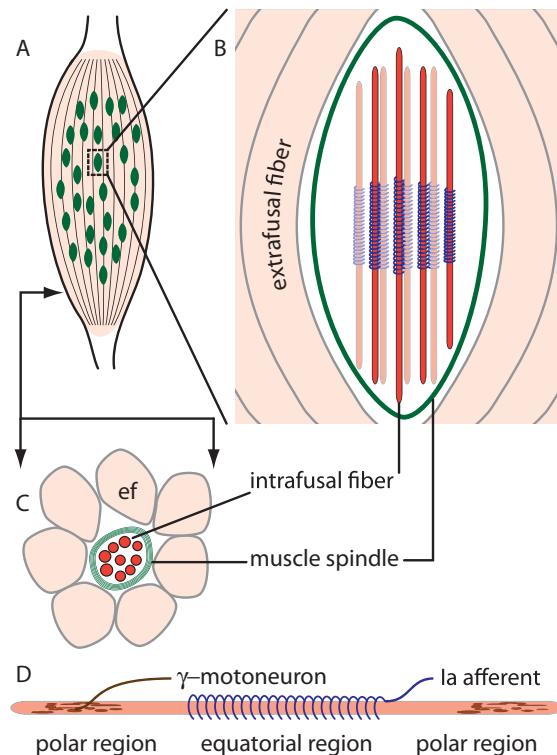
peripheral structure called a **muscle spindle**. A muscle spindle is a capsule containing a group of **intrafusal fibers** that are stretched passively when the whole muscle stretches (Fig. 22-1). In contrast to the **extrafusal** muscle fibers that produce the force of muscle contraction, intrafusal fibers:

- Are very thin and short
- Do not contribute to the force of contraction
- Are fewer in number than extrafusal muscle fibers

Intrafusal fibers are oriented parallel to the extrafusal fibers of a muscle. Each intrafusal fiber receives sensory innervation from a stretch-sensitive Ia afferent fiber. Ia afferents that sense the stretch of intrafusal fibers have myelinated axons that conduct action potentials *rapidly* at 70 m/s or more in humans, allowing for the quick transmission of information regarding unexpected loads. *Spindle afferents weave around the central region of an intrafusal fiber to sense the amount and rate of stretch in the intrafusal fibers.* The central or **equatorial** portion of an intrafusal fiber does not contract at all but rather is passively stretched by load-elicited changes in muscle length (Fig. 22-1D).

Intrafusal fibers also receive motor innervation from a special type of motoneuron, termed the **γ -motoneuron**. To distinguish the motoneuron that we have discussed heretofore from the γ -motoneuron, the type of motoneuron that innervates

Figure 22-1. Intrafusal fibers are modified skeletal muscle fibers that do not stretch the length of the muscle, as extrafusal fibers (ef) do. Intrafusal fibers do not contribute to the force produced by skeletal muscle contraction but rather house muscle stretch receptors. Groups of intrafusal fibers are contained in a capsule called the muscle spindle. **A:** Muscle spindles (green oblongs) are scattered throughout skeletal muscle. **B:** A tangential view of a muscle spindle surrounded by extrafusal fibers is shown. **C:** A cross-section through a muscle spindle shows that the diameters of intrafusal fibers are much smaller than those of extrafusal fibers. **D:** Each intrafusal fiber contains an equatorial region surrounded by two polar regions. A mechanoreceptive sensory afferent called the Ia afferent weaves around the equatorial region of an intrafusal fiber. Stretch of this middle portion of the intrafusal fiber excites the Ia afferent. The polar regions of intrafusal fibers are contractile and contract in response to input from a γ -motoneuron.

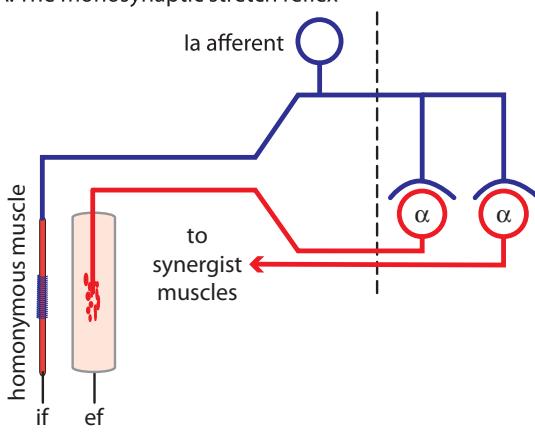


extrafusal fibers is called an α -motoneuron. Note that the unqualified term *motoneuron* always refers to the α -motoneuron rather than the γ -motoneuron. The γ -motoneuron contacts the intrafusal fiber at its **polar** ends where contraction is possible (Fig. 22-1D). As discussed below, the contraction of the polar ends of the intrafusal fibers functions to stretch the equatorial portion of the intrafusal fibers and does not generate sufficient force to contribute to movement or load-bearing.

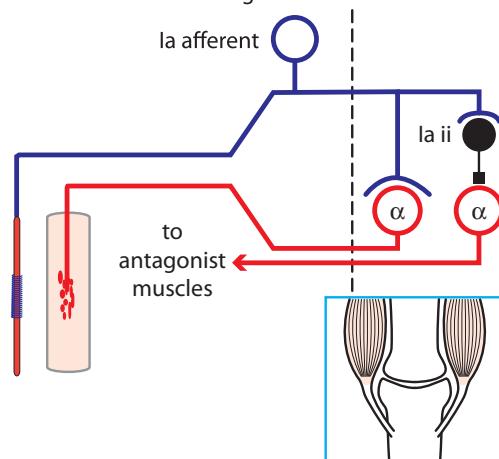
Ia afferents enter the spinal cord through the dorsal root and course ventrally to synapse directly onto all of the α -motoneurons of the same or **homonymous** muscle and onto many of the motoneurons that innervate its **synergists**, meaning muscles that act at the same joint and pull in the same direction (Fig. 22-2A). When a load stretches a muscle, muscle spindles and the intrafusal fibers within are stretched, eliciting a barrage of impulses that travel up Ia afferent fibers. Ia afferent activity, in turn, directly excites motoneurons that innervate the homonymous muscle and motoneurons that innervate synergists. The resulting contraction of homonymous and synergist muscles opposes the original stretch. In general, the stretch reflex is strongest in muscles that oppose gravity, termed **physiological extensors**, thus helping to maintain postural control (see Box 22-3). The stretch reflex can be tested in humans using minimally invasive techniques; such reflex testing provides a powerful diagnostic tool (see Box 22-4).

Figure 22-2. The essential circuits of the stretch reflex are diagrammed. A minimum of anatomical details are illustrated in order to most clearly convey the essential circuitry. More anatomical detail on the spinal cord is included in Chapter 9. **A:** Two types of neurons form the fundamental stretch reflex circuit. The endings of Ia afferents wrap around intrafusal fibers (if) and sense stretch. Ia afferents cross from the periphery into the central nervous system (dotted line) and directly contact α -motoneurons (α) that project into the periphery to innervate extrafusal fibers (ef) in the same or homonymous muscle, as well as in synergist muscles. Synergist muscles are those that work in concert to produce the same action. The fundamental stretch reflex circuit contains one central synapse, the synapse from the Ia afferent to an α -motoneuron. **B:** Muscle stretch also results in the inhibition of antagonist muscles. The inhibition of antagonist muscles is accomplished through activation of the glycinergic Ia inhibitory interneuron (Ia ii). The inset (blue box) shows an agonist–antagonist pair of muscles. The members of an agonist–antagonist muscle pair move a joint in opposing directions.

A. The monosynaptic stretch reflex



B. The stretch reflex + antagonists



THE CONTROL OF MUSCLES THAT WORK WITH AND OPPOSE GRAVITY IS ORGANIZED DIFFERENTLY.

The terms *extensors* and *flexors* refer to muscles that *increase* and *decrease*, respectively, a joint angle. For example, the quadriceps are knee extensors and the biceps femoris, a big portion of the muscle mass commonly referred to as the hamstring, is a knee flexor. Although this classification scheme is straightforward, consider the effect of quadriceps or biceps femoris muscle contraction on the hip joint. The quadriceps, a knee extensor, is a hip *flexor*, whereas the biceps femoris, a knee flexor, is a hip *extensor*. Thus, the terms extensor and flexor—as defined by joint angle—are not robust, reliable, or consistent terms.

The terms *physiological extensors* are muscles that, when contracted, oppose gravity, and **physiological flexors** are those that work in concert with

gravity. Jaw-closing muscles, such as the masseter or temporalis, elevate the jaw against gravity and thus are physiological extensors, even though their activation decreases joint angle. The terms of physiological extensors and flexors are robust in that they are invariant across different joints: the quadriceps, whether extending the knee or flexing the hip, oppose gravity. Furthermore, motor circuits are organized around physiological extensors and flexors rather than around joint extensors and flexors. To stay upright and to avoid a permanently slack-jawed appearance, brainstem motor centers project to the spinal cord (see Chapter 23) and tonically excite *physiological extensors*—not joint extensors. Thus, *motor circuits respect a classification of muscles according to their work with respect to gravity*.

When a muscle is stretched, and the homonymous muscle contracted, activity in muscles that oppose contraction of the homonymous muscle is inhibited. Inhibition occurs via a synapse from the Ia afferent onto an inhibitory interneuron that in turn inhibits motoneurons innervating the antagonist muscle (Fig. 22-2B). The Ia afferent-to-inhibitory interneuron-to-antagonist motoneuron circuit is the basis for **reciprocal inhibition**. This pathway is disynaptic, since it involves two synapses—the first between the Ia afferent and the inhibitory interneuron, and the second between the inhibitory interneuron and the motoneuron. The inhibitory interneuron in this case is such an important cell that it has its own name: the **Ia inhibitory interneuron**. The Ia inhibitory interneuron contains **glycine**, the second most prevalent fast inhibitory neurotransmitter, behind γ -aminobutyric acid (GABA), and the most prevalent one in the spinal cord.

γ -MOTONEURONS ENSURE THAT THE STRETCH REFLEX IS ONLINE DURING ACTIVE MUSCLE CONTRACTION

The stretch reflex is not only interesting because it is a monosynaptic reflex but also because it illustrates an important element in motor control—the role of peripheral feedback. In order to make movements correctly, motoneurons need to receive input on the *current* state of the muscles: their length, rate of

REFLEX TESTING IS A MINIMALLY INVASIVE PROCEDURE THAT TESTS THE INTEGRITY OF THE STRETCH REFLEX CIRCUIT.

In **reflex testing**, an electromyogram (EMG) recording electrode is placed in a muscle, and a stimulating electrode is placed in the nerve leading to that muscle (Fig. 22-3A). At the lowest effective stimulating intensities, Ia afferents are activated (Fig. 22-3B). After some delay, 5–30 ms depending on how far the stimulating electrode is from the muscle, a muscle contraction occurs. The pathway taken is Ia activation → α -motoneuron excitation → muscle activation recorded by the EMG electrode. This is the **H reflex**.

When the stimulation intensity is increased, motor axons are directly activated, and a muscle action potential occurs at very short latency (<5 ms)—this is called the **M response**—after which the H reflex occurs (Fig. 22-3C). Note that this sequence occurs only after increasing the stimulation intensity because motoneuron axons have a greater electrical threshold for activation than do Ia afferent axons. When the stimulation intensity increases even farther, the M response grows and the H reflex shrinks until only the M response occurs. Try to work your way through why this happens.

Hint: Remember that when you stimulate an axon, action potentials travel in both directions.

To understand the spoiler, we need to define two terms regarding how action potentials travel. **Antidromic** refers to the wrong direction or the direction that is counter to the normal direction of action potential traffic. **Orthodromic** is the right direction, the direction of normal action potential traffic.

Now, here is the spoiler. As the stimulation intensity increases above the threshold for activating

motoneuron axons, more and more motoneuron axons are activated along with the full complement of Ia afferents. An action potential in a motoneuron axon travels both orthodromically to the muscle, producing the M response, and antidromically to invade motoneuronal somata in the spinal cord (Fig. 22-3D). Meanwhile, action potentials in Ia afferents travel orthodromically to the spinal cord to synapse on homonymous motoneurons. However, action potentials arriving antidromically from motoneuron axons reach the motoneuronal somata before action potentials arriving orthodromically from Ia afferents. This is because (1) motoneuron axons conduct action potentials more rapidly than do Ia afferents and (2) more importantly, because it takes time to cross a synapse. Recall that the synaptic delay is about a half millisecond. Therefore, although an action potential in a Ia afferent axon reaches the Ia afferent terminal quickly, it does not affect the motoneuron until after a synaptic delay. The upshot of this arrangement is that by the time that the Ia afferent action potential excites the motoneuron, the motoneuron is still in the absolute refractory period from the action potential that arrived antidromically from the motoneuron axon. Consequently, the motoneuron cannot fire an action potential in response to Ia afferent input. In this way, action potentials that travel antidromically *occlude* or *collide* with action potentials arriving orthodromically. When *all* the motor axons are activated, the maximal M response occurs, and the action potentials in the motor axons traveling centrally invade all of the motoneurons, thereby blocking the H reflex from occurring at all.

lengthening or shortening, and whether they are contracting or relaxing. The Ia afferent innervation of muscle spindles provides some of this information.

As explained above, activity in α -motoneurons leads to contraction of extrafusal fibers, but not intrafusal fibers. This presents an immediate problem: if a muscle contracts and the intrafusal fibers do not contract, the intrafusal fibers will become slack (Fig. 22-4A-B). In a slack configuration, no change in muscle length can be signaled by the spindle receptors. It is therefore crucial that the intra- and extrafusal fibers are the same length at all times. γ -Motoneurons serve to ensure this by synapsing on the

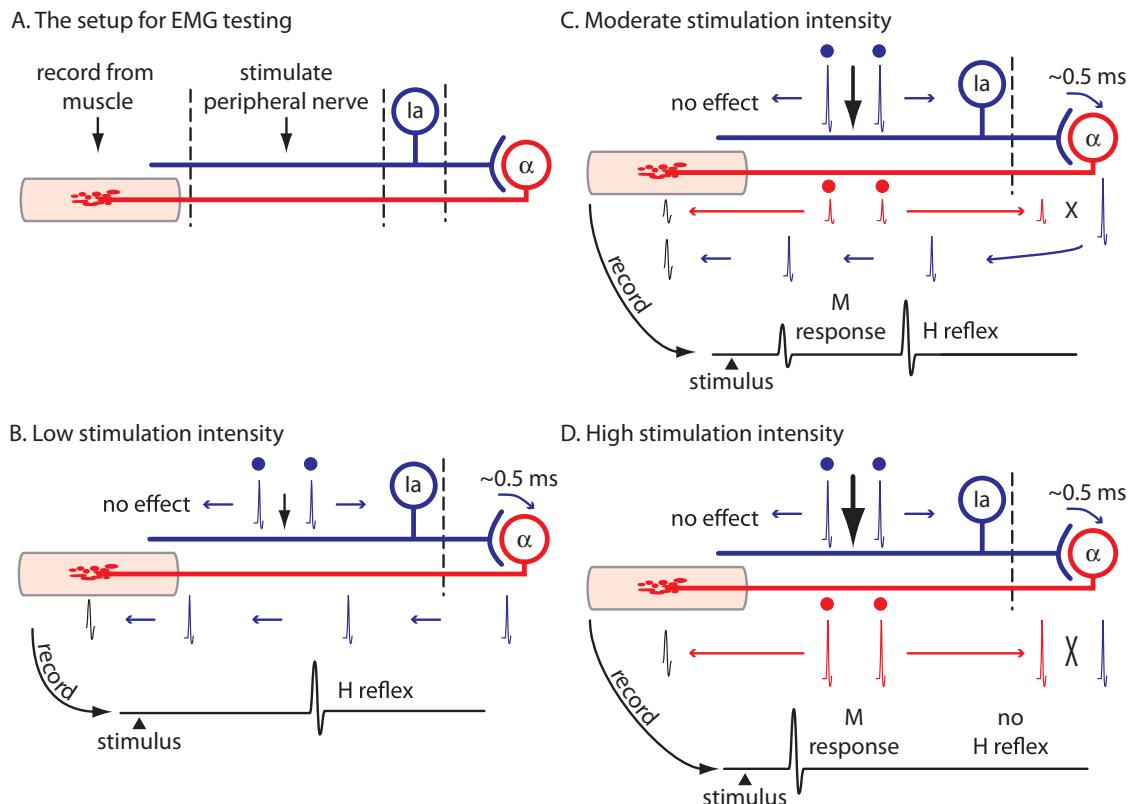


Figure 22-3. The basic setup and ideal results of electromyography, or EMG, testing are illustrated. **A:** Electrical stimulation of a peripheral nerve has the potential to excite the axons of la afferents (blue labeled la) and motoneurons (red labeled α). The effect of nerve stimulation on muscle activity is measured using EMG recording from the muscle. **B–D:** The height of the action potentials is proportional to the number of axons excited. **B:** At the lowest stimulation intensities (small black arrow), only la afferents are excited. Electrical stimulation produces action potentials that travel away from the stimulation electrode toward either side. Action potentials that result directly from stimulation are denoted by a filled circle above. The action potentials in la afferents that travel toward the muscle have no effect. The la afferent action potentials that travel orthodromically toward the spinal cord lead to the excitation of α -motoneurons after a synaptic delay of about a half millisecond. Excitation of α -motoneurons leads to a muscle contraction after a delay of several milliseconds, depending on conduction distance to the muscle. This muscle contraction is termed the *H reflex*. **C:** At moderate stimulation intensities (medium black arrow), more la afferent axons along with some motoneuron axons are excited. Action potentials are color coded according to whether they occur as a result of excitation of la afferent axons (blue) or of motoneuron axons (red). Electrical stimulation produces action potentials that travel away from the stimulation electrode on either side of both la and motoneuron axons. The orthodromically traveling action potentials in motoneuron axons reach the muscle and elicit a muscle contraction. This is termed the *M response*. The M response occurs much earlier than the H reflex because: (1) there is no synaptic delay; and (2) the conduction distance and time are far less. There are also action potentials that travel antidromically in the motoneuron axon. These action potentials collide with action potentials arising from the synaptic responses in motoneurons to la afferent input. Since action potentials that collide (*x*) do not continue on, only a portion of the action potentials continue to travel orthodromically in the motoneuron axons. The result is a small M response followed by an H reflex. **C:** At the highest stimulation intensities (large black arrow), all la afferent and motoneuron axons are excited. Therefore, all of the action potentials arising from synaptic responses in motoneurons to la afferent input collide with action potentials traveling antidromically in the motoneuron axon (*large x*). Consequently, there is a large M response and no H reflex.

polar regions of intrafusal muscle fibers. When a γ -motoneuron fires, the innervated intrafusal muscle fiber shortens in length.

During most reflex and voluntary movements, α and γ -motoneurons are coactivated. This α - γ coactivation mandates that the intrafusal and extrafusal muscle fibers are maintained at similar lengths (Fig. 22-4C). γ -Motoneurons lie in the same motoneuron pools with α -motoneurons innervating the same muscle. Neurons important in self-generated movements, particularly axons descending from brainstem and cortex typically synapse on γ -motoneurons, as well as on α -motoneurons. This circuitry ensures that muscle spindles are ready to signal any changes in muscle

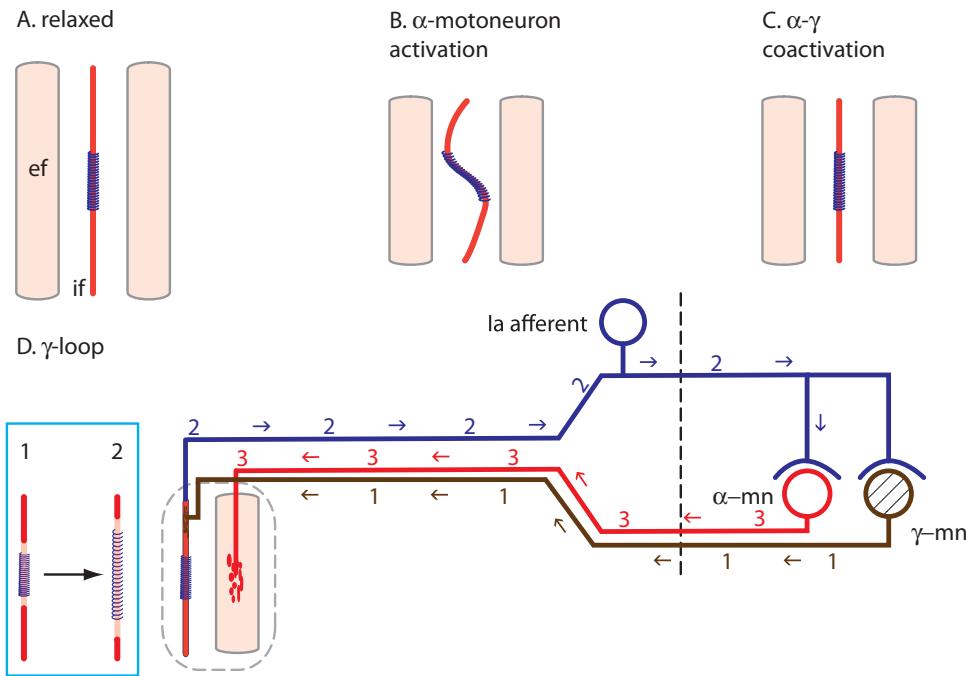


Figure 22-4. **A:** In the relaxed state, intrafusal fibers (*if*) are taut and sensitive to stretch. However, if an α -motoneuron were to be activated alone (**B**), the extrafusal fibers (*ef*) would contract but the intrafusal fibers would go slack. In this situation, a load would have no effect on an intrafusal fiber. Consequently, Ia afferents would go “off-line” as they could no longer sense stretch. **C:** α - γ coactivation resolves this problem by maintaining the intra- and extrafusal fibers at matching lengths. **D:** The γ loop starts with γ -motoneuron (γ -mn) activation (brown arrows marked 1). The effect of γ -motoneuron activation is contraction of the polar ends of the intrafusal fibers (see inset in blue box). Contraction of the polar ends of the intrafusal fibers stretches the equatorial region of the intrafusal fibers, resulting in Ia afferent activation (blue arrows marked 2). Ia afferent activation leads to excitation of α -motoneurons (α -mn). Activity in α -motoneurons (red arrows marked 3) leads to extrafusal fiber contraction and muscle tension. Thus, the γ -loop starts with γ -motoneuron activation and culminates in muscle tension that is dependent on sensory activity in Ia afferents.

length, due to unexpected stretches or loads, that occur throughout any voluntary or self-generated motion.

ACTIVATION OF γ -MOTONEURONS ALONE CAN LEAD TO MUSCLE CONTRACTION

One result of the stretch reflex circuitry is that *by activating γ -motoneurons alone, one can indirectly excite α -motoneurons: this is called the γ -loop* (Fig. 22-4D). We go through this step by step:

1. γ -Motoneuron activity contracts intrafusal fibers at the polar regions.
2. Contraction of the intrafusal fibers at the poles pulls at both ends of the central region of the intrafusal fiber.
3. Stretch of the central portion of the intrafusal fiber excites Ia afferents.
4. Activity in Ia afferents excites α -motoneurons innervating the homonymous muscle.

In sum, the γ -loop starts with excitation of a γ -motoneuron and ultimately results in muscle contraction (Fig. 22-4D).

The γ -loop is conceptually important. Some motor control centers in the brainstem preferentially excite γ -motoneurons over α -motoneurons. Upon selective or preferential activation of γ -motoneurons, tension of the intrafusal fiber increases, thereby increasing the sensitivity of the Ia afferents and the **gain** of the stretch reflex (see Box 22-5). This means that when γ -motoneurons are activated, any given stretch elicits a larger contraction. *An increase in the gain of the stretch reflex may be particularly useful when delicate movements are being performed in unpredictable environments.* For instance, when walking on ice, extreme sensitivity to even the minutest slippage—which inevitably stretches extensors—may prevent a serious fall and resulting injury. After damage to the forebrain, brainstem postural centers excite extensor γ -motoneurons, initiating extensor muscle contractions via the γ -loop. This produces a condition of extensor **spasticity**—spasticity denotes a tonic muscle contraction that resists passive movement—which for historical reasons is misleadingly known as **decerebrate rigidity**.

ACTIVATION OF TENDON RECEPTORS DISYNAPTICALLY INHIBITS CONTRACTION

A second muscle reflex, the **inverse stretch reflex** or **inverse myotactic reflex**, is a **disynaptic** reflex, meaning that it involves two synapses and three neurons. The inverse stretch reflex is engaged during active contraction to oppose the contraction itself. Although this may appear counterproductive at first glance, this reflex serves a number of purposes, including protecting muscle injury from overcontraction during very forceful movements.

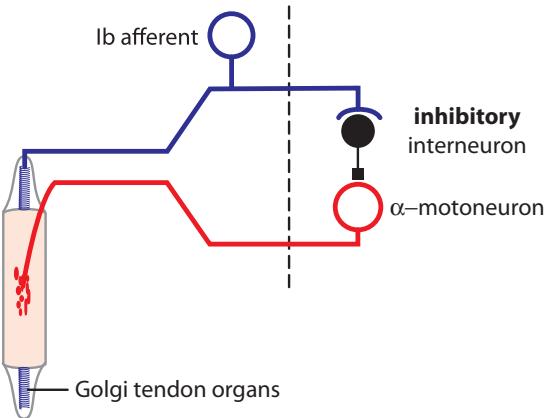
Box 22-5

THE GAIN OF THE STRETCH REFLEX VARIES ACROSS DIFFERENT CONTEXTS.

Gain is the ratio of output to input. In the case of the stretch reflex, gain refers to the amount of homonymous muscle shortening per stretch of that muscle. For example, if a muscle is stretched by 5 mm, and the stretch reflex contracts the muscle by 3 mm, the gain of this reflex would be $3/5$ or 0.6. When the gain of a reflex equals 0, the reflex is fully suppressed. When the gain of a reflex is 1, the reflex acts as a

perfect **servomechanism**, meaning that the reflex responds to a stretch with an opposing contraction of equal magnitude. The gain of the stretch reflex and of other reflexes varies across conditions such as sleep, wake, exercise, walking, and so on. In addition, many motor disorders are associated with either an increase or decrease in reflex gain.

Figure 22-5. Ib afferents weave in and out through the Golgi tendon organs located at the junction of tendon and muscle. During active contraction, but not during passive stretch, the Golgi tendon organs are stretched and Ib afferents are excited. Ib afferents excite inhibitory interneurons, which in turn inhibit homonymous α -motoneurons.



The inverse stretch reflex depends on the **Ib afferent**, another fast-conducting proprioceptive receptor like the Ia afferent (Fig. 22-5). The endings of the Ib afferent weave in and among the **Golgi tendon organs** formed by a tendon's collagen fibers located at the junction between tendon and extrafusal fiber. *Ib afferents are excited by tension generated by muscle contraction rather than by passive stretch. Activation of Ib afferents by muscle tension inhibits homonymous and synergist α -motoneurons while exciting antagonist α -motoneurons.* Interneurons in the ventral horn indirectly mediate both the inhibition and excitation produced by Ib afferents (Fig. 22-5). Thus, Ib afferents excite excitatory interneurons that in turn excite antagonist α -motoneurons. Ib afferents also excite inhibitory interneurons that inhibit homonymous and synergist α -motoneurons.

Ib afferent-mediated inhibition of α -motoneurons serves to dampen increases in muscle tension (i.e., increase stiffness). The strength of the Ib afferent-mediated reflex is regulated by input from local interneurons and supraspinal sources. Thus, when a great deal of force is required, Ib afferent-mediated inhibition can be turned down, turned off, or even reversed, allowing large increases in muscle tension to occur without feedback inhibition. For instance when trying to hit a home run, the Ib reflex is suppressed. In contrast, when a highly controlled touch is required, as during threading a needle, the strength of the Ib reflex can be increased.

Ia and Ib afferents are both excited by changes in muscle but their response characteristics are distinct. Ia afferents respond to *passive stretch* of the muscle spindles, such as occurs when a load is added to a muscle, but do not respond to active contraction. In contrast, Ib afferents respond to stimulation of the Golgi tendon organs during active muscle contraction but do not respond to passive stretch.

POTENTIAL INJURY ELICITS PROTECTIVE REFLEXES

The **nociceptive withdrawal reflex** serves an important protective function as it rapidly removes a body part from harm's way. This reflex occurs automatically and without conscious direction, as when one yanks a hand away

from a flame. Yet, the nociceptive withdrawal reflex is beguilingly structured in a way that reveals fundamental principles of spinal cord organization.

Consider that you step on a thorn with your heel or with the ball of your foot, or with your little toe. In all cases, a withdrawal occurs. However, the withdrawal is *tailored* to the location of the stimulus. Thus, the heel is removed from the ground in the case of a thorn in the heel, the toe is withdrawn in the case of a thorn in the toe, and so on. For example, stimulation on the ball of the foot leads to reflex activation of the soleus muscle, and activation of the soleus muscle then *removes* the ball of the foot from the ground. Similarly, heel stimulation leads to reflex activation of the tibialis anterior muscle, which in turn leads to the heel being lifted from the ground. In this way, the area of stimulation matches the area of withdrawal. Put in other terms, the *withdrawal* field of the nociceptive withdrawal reflex overlaps the receptive field.

The nociceptive withdrawal reflex is a polysynaptic circuit that involves a minimum of two central neurons. One of the necessary central neurons is, of course, a motoneuron. The other neuron required for the nociceptive withdrawal reflex is an interneuron that we will call a *reflex encoder*. Reflex encoding neurons are present in the deep dorsal horn. They receive input from a variety of sensory afferents, both nociceptors and A β mechanoreceptors, and they target the motoneurons to specific muscles. The sensory input to reflex encoders is weighted proportionally to the withdrawal or unloading action of the targeted muscles. For example, a reflex encoder that targets soleus motoneurons weights sensory input from the ball of the foot far more than input from the heel, and the withdrawal field produced by soleus muscle activation is centered over the ball of the foot (Fig. 22-6A). In sum, the nociceptive withdrawal reflex transforms sensory input into a muscle-centric signal. Consequently, reflex encoders within the dorsal horn are organized topographically by muscle, termed **musculotopic**, rather than somatotopically by skin area. It is remarkable that a movement as fundamental as the nociceptive withdrawal reflex is *learned* during development (see Box 22-6).

CENTRAL CIRCUITS CAN GENERATE PATTERNED MOVEMENT SEQUENCES

Whenever we walk, whether across a carpet or an icy and uneven field, the core fundamentals of our walk remain the same. The confident walk on carpet and the tentative one on ice share a single basic gait of alternating leg steps. What generates this and other fundamental movement patterns? These fundamental movements are too complicated to be a reflex, or even a chain of reflexes. Indeed, the basic gait pattern and other movement fundamentals *do not depend on sensory feedback from the periphery* and therefore cannot depend on reflex function. On the other hand, gait and other core movements happen semiautomatically, far too thoughtlessly to involve deliberate or volitional control at each step. As a neural compromise, *circuits within the spinal cord and brainstem, termed central pattern generators, generate the core element of rhythmic and repeated movements such as walking, swallowing, chewing, and micturition.*

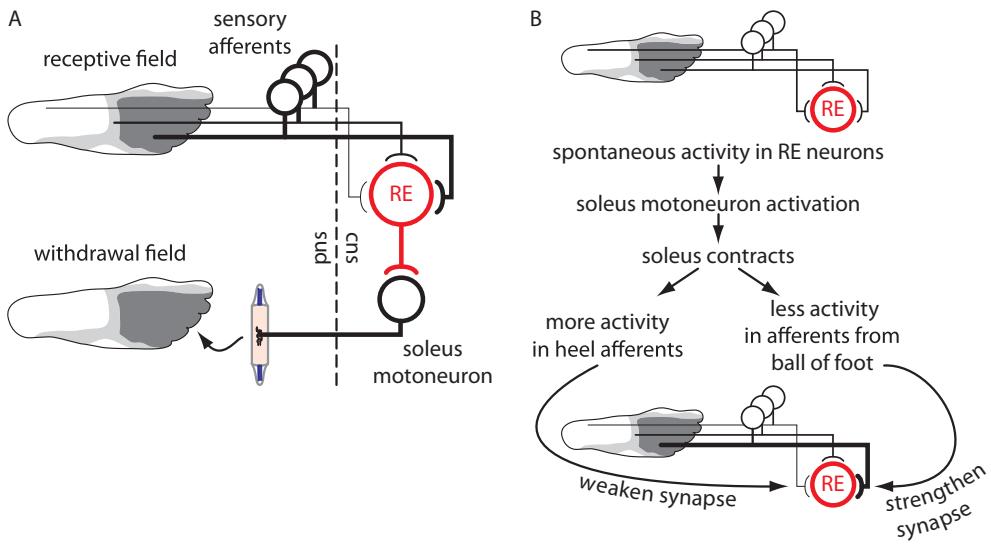


Figure 22-6. A: Sensory afferents from the foot synapse on reflex encoder neurons (RE) in the deep dorsal horn. The input from different areas of the foot arrives via synapses of different weights (proportional to the width of the line). The most heavily weighted inputs to reflex encoders are from areas of skin that are withdrawn by the contraction of the motoneurons targeted by those reflex encoder neurons. In this way, the receptive field of a reflex encoder neuron maps onto the withdrawal field produced by activation of the same reflex encoder neuron. B: At birth, inputs from wide areas of the skin make equally weighted synapses on reflex encoder neurons. During sleep, a spontaneous burst of activity in a reflex encoder neuron leads to contraction of the targeted muscle. The synapses from afferents that increase their activity after muscle contraction are weakened or eliminated. In contrast, synapses from afferents that decrease their activity after muscle contraction are strengthened. This process of somatosensory imprinting leads to mature circuits in which receptive and withdrawal fields overlap.

Modified from Schouenborg, J. Action-based sensory encoding in spinal sensorimotor circuits. *Brain Res Rev* 57: 111–17, 2008 with permission of the publisher, Elsevier; and from Sonnenborg, F.A., Andersen, O.K., and Arendt-Nielsen, F. Modular organization of excitatory and inhibitory reflex receptive fields elicited by electrical stimulation of the foot sole in man. *Clin Neurophysiol* 111: 2160–9, 2000, with permission of the publisher, Elsevier.

Box 22-6

WITHDRAWAL REFLEX CIRCUITS ARE ADAPTIVELY ORGANIZED DURING SLEEP IN INFANCY.

There is little somatotopy in the organization of afferent input to dorsal horn cells at birth. Afferents from widespread areas of skin synapse on reflex encoding neurons. Moreover, afferent synapses from widespread areas of the skin are equally weighted (Fig. 24-6B). This rudimentary organization sets the stage for a process called **somatosensory imprinting** by which synaptic inputs from sensory afferents to reflex encoders become accurately weighted to produce effective and adaptive withdrawal reflexes. Remarkably, much of somatosensory imprinting appears to occur during active sleep in neonates.

Some spontaneous movements, simple twitches and the like, occur during active sleep. At least some

of these spontaneous movements stem from spontaneous activity in reflex encoders (Fig. 24-6B). As reflex encoders are already connected to specific motoneuron pools, activity in a reflex encoder leads to muscle contraction. The key to somatosensory imprinting is the strengthening of sensory inputs that are *reduced* by correlated muscle contraction and the weakening or elimination of synapses from sensory inputs that fire more after muscle contraction. The result of the synaptic modifications produced by somatosensory imprinting is that nociceptive input leads to contraction of the muscles that maximally withdraw the affected body part from the stimulus.

Central pattern generators create a patterned activation and relaxation of specific muscles through selective central connections and can do so in the absence of peripheral feedback or supraspinal input. Yet, central pattern generators cannot produce fully elaborated versions of rhythmic and repeated movements without input from the periphery *and* the participation of reflexes. Further, input from the brainstem, cerebellum, and cerebral cortex tweak movements resulting from central pattern generator activity into recognizable motions. In other words, movements generated solely by central pattern generator activity would bear little resemblance to the same movements generated by an intact nervous system with working reflexes, connections to the periphery, and input from modulatory circuits.

The actual neuronal elements that comprise a central pattern generator are interconnected neurons that form a circuit. Our understanding of central pattern generator function stems in large part from experiments in invertebrates and also from experiments in early vertebrates such as the jawless lamprey. These basic investigations have demonstrated that *a single circuit can be reconfigured to produce multiple related movements.* In the mammal, this means that a single circuit serves walking and running or chewing and sucking. An important limitation to the central pattern generator concept as it is applied to humans is that we do not know the exact boundaries of human central pattern generator circuits, nor can we enumerate the neuronal elements that comprise central pattern generator circuits. Thus, central pattern generator circuits, particularly those in humans, are better established as conceptual framework than as specific anatomical reality.

To better understand the control of semiautomatic movements, we examine walking in some depth because it is both exemplary and important:

- All parts of the motor system participate, in characteristic ways, in producing walking. Examining each region's contribution to walking will illuminate that region's general mode of operation.
- Locomotion is an integral human function, which, when impaired, leads to a severe compromise of a person's quality of life. In other words, people are fairly unhappy if they lose their ability to get around.

HUMAN LOCOMOTION REQUIRES FORWARD PROPULSION WHILE REMAINING BALANCED ON TWO LIMBS

Locomotion in humans is different from locomotion in other animals because we face the dual challenge of (1) staying upright and (2) advancing forward. Thus, successful locomotion requires postural stability, provided by the brainstem, as well as some form of propulsion, typically termed *gait*, that arises from spinal circuits. In the following section, we examine gait, and in the next chapter, postural control is discussed.

Normal human gait involves stepping movements controlled by central pattern generators in the spinal cord. To best understand gait, we examine the gait cycle, from its most elemental component—the movements of one leg—to its most integrative—coordination of the two legs with trunk and arm movements.

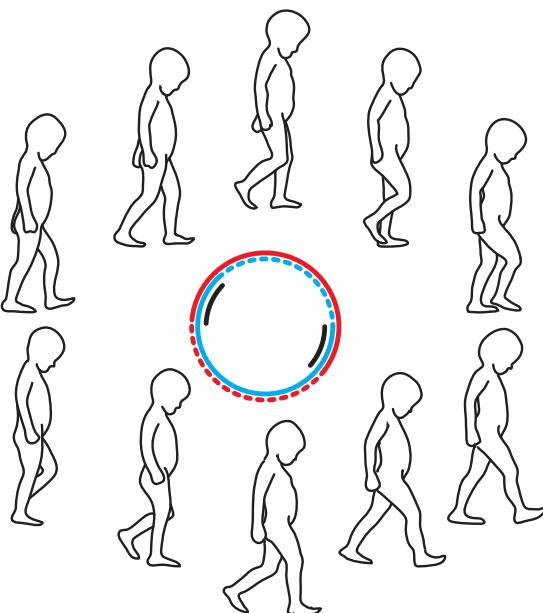
Each leg cycles between swing and stance during locomotion (Fig. 22-7):

- In the **swing** phase, the foot is not in contact with the ground.
 - To initiate the swing, the hip and knee flex, lifting the toes off the ground.
 - The leg advances forward to a point ahead of the body.
- During the **stance** phase, the foot is in contact with the ground, providing support to the body.
 - To begin the stance, the leg extends and the heel lands on the ground, termed **heel strike**.
 - Weight is loaded onto the extended leg, which flexed at the knee, acts as a spring, accepting the load.
 - At mid-stance, the knee straightens and the leg, positioned directly below the body with a flat foot, supports the entire weight of the body.
 - The leg is extended backward, propelling the body forward. The foot rolls forward on to the toes, ready for lift-off, as the other leg touches down to begin a period of **double support**.

During locomotion, each leg cycles repetitively through stance and swing phases. During walking, the movements of the two legs are coordinated so that after one leg contacts the ground, the other leg lifts off. In the moments intervening between heel strike on one side and lift off on the contralateral side, both feet are in

Figure 22-7. The walking cycle of a young infant is illustrated. The cycle proceeds in a clockwise direction. This child's gait is not fully mature, but shows the essential features of human locomotion. Each leg alternates between stance (solid lines in the circle) and swing (dotted lines). Stance starts at heel strike and swing starts with lift off. For example, the left leg (red) begins the stance phase with a heel strike as the right leg (blue), is still in contact with the ground. Weight transfers to the left leg as the body is propelled forward. As the left leg assumes the weight of the body, the right leg begins the swing phase and so on. Between the left and right legs' swings, both legs are in contact with the ground, a period of double support (black arcs). The immaturity of the gait is evident in the minimal arm swing, the downward head posture, and less ankle flexion than is typically present in a healthy adult.

Modified from Muybridge, Eadweard. *The human figure in motion: An electro-photographic investigation of consecutive phases of muscular actions*. London: Chapman & Hall, 1904.



contact with the ground. During this time of *double support*—in total about 60% of the walking cycle—the weight of the body shifts from the leg that is about to lift off to the leg that has just landed. As the leg that is about to lift off swings forward, the contralateral leg moves to a position directly underneath the body. Trunk and arm movements are coordinated with alternating leg movements during locomotion.

Although the core movements involved in walking are stereotyped, walking varies with speed (see Box 22-7), it varies across the life cycle (see Box 22-8), individuals, and circumstances. When children learn to walk, they begin with a characteristically different gait, and as age takes its toll on joints, muscles, and vim, we alter our gait again. At a distance of a block, we recognize friends and even can tell something about their mood. We discern this information by recognizing a friend's individual and distinctive gait rather than by making out the details of that friend's face. As another example of gait changing with circumstances such as mood, fatigue, injury, and motivation, compare a teenager's gait when walking to the principal's office after being caught passing notes in class, shoulders slumped and rotating minimally, with the same individual's gait when walking up to deliver a valedictorian speech, shoulders back and torso rotating in full swagger.

CENTRAL PATTERN GENERATORS GENERATE A BASELINE MOVEMENT THAT IS MODIFIED BY EXTERNAL AND INTERNAL CUES

Box 22-7

RUNNING REPRESENTS A VARIANT OF THE WALKING PATTERN.

During running, the support phase decreases in duration, so that one leg lifts off while the other is still swinging, resulting in the body being airborne for a time. With increasing speed, the support period progressively shortens, the length of time airborne increases, and greater muscle force is used to propel the body forward.

Central pattern generators in the lumbar spinal cord generate a rudimentary version of gait. A circuit on each side produces the fundamental pattern of a leg stride and commissural connections between the sides provide basic coordination between the two legs. By alternating the strength of synaptic connections within the central pattern generator, the same spinal circuit that produces a walking gait, differently configured, can give rise to related movements such as crawling, skating, the kicking component of the crawl stroke, and of course, running. Thus, by modulating the connectivity and level of excitation within one basic, step-producing circuit, not one, but a multitude of gaits becomes possible. One weird-but-true consequence of this organization is that the cerebellum can engage circuits on either side of the cord such that the two legs walk at different speeds or even in *different directions* when on a treadmill with two independently controlled half-belts (more about this in Chapter 24).

The spinal central pattern generator for gait does not operate solo and indeed needs an external trigger to be initiated. A region in the midbrain, the **mesencephalic locomotor region**, provides the start signal to gait-producing circuits in the spinal cord. As the output of the mesencephalic locomotor region increases, the locomotion generated increases in speed, from a slow to a faster and faster walk and eventually to a jog, a run, and a sprint. Using this flexible arrangement, the midbrain and lumbosacral cord work together to produce locomotion at different speeds by adjusting the strength of the intervening signal.

WALKING IS A PLASTIC MOTOR PATTERN THAT CHANGES DRAMATICALLY ACROSS A NORMAL LIFESPAN.

The riddle of the Sphinx; “Which creature in the morning goes on four feet, at noon on two, and in the evening upon three?”

The answer, provided according to mythological legend by Oedipus, who interpreted time of day as a metaphor for time in life cycle, is a human. A baby crawls on four feet before learning to walk on two and until needing a third leg, or cane, to ambulate. That is to say that walking proceeds through a series of predictable changes as a person develops and then ages. *When babies, top heavy with their disproportionately large heads, first begin to walk while holding on to objects to provide balance, they walk in a side-to-side waddle with little forward motion. The arms are held up, used entirely for balance, and do not swing. The legs are held fairly rigidly, particularly at the ankle, and the initial touch down is on either the toes or a flat foot.* An infant’s walk involves no true swing phase but rather consists mainly of double support, briefly interrupted by lifting of alternating legs. Each leg leaves the ground, raised from the hip en masse, and “plops” down shortly thereafter. As an infant’s ability to maintain balance matures, the ability to walk independently is gained. By 3 years old, a relatively mature walk is in place, complete with a heel strike upon touch down and alternating arm motions.

Walking is learned, and that is very important. Apparently by instinct, all babies get the itch to move themselves about in the world, but they have to *learn* this skill. What advantages emerge from a baby’s learning to walk rather than simply being born with the innate ability to walk? One advantage is that babies born with a physical anomaly can learn an effective, albeit different, method for ambulating. Think of conjoined twins. If at all possible, conjoined twins will find a way to ambulate, something that would be impossible with a rigid, inborn program for walking wholly inappropriate to the twins’ anatomy. A second, probably more important, advantage stems from the fact that one must lead either a very short or a very charmed life to avoid any injury that impacts walking. Whether it be a pulled muscle, a broken bone, or a central nervous system disease, things happen in a typical life. Yet, for the most part, people learn, perhaps using

similar learning circuits to those used in infancy, to adjust their locomotor pattern to achieve their ambulatory goals. For infants, practice plays a critical role in learning to walk. Infants walk for hours each day, traveling on average 1.6 miles (2.7 km), equivalent to more than 8 miles (13 km) if their strides were of average adult length. Given the intensity of infants’ walking repetition, one may wonder whether intense practice rather than immobility would better serve people trying to recover after injury.

An unfortunate exception to the generalization that people compensate for injuries and continue to move about is spinal cord injury. One of the first questions that a patient with spinal cord injury typically asks is, “Will I ever walk again?” Right now, the answer, for someone with a complete or nearly complete transection, is typically no, at least not in the same way as before the injury. For one, bipedal walking requires balance which, as discussed in the next chapter, requires a *connection* from the brainstem to the spinal cord, a connection that is interrupted by severe spinal cord injuries. It is reasonable to ask whether gait would be possible if balance and an upright posture were assured. Consistent with the presence of a central pattern generator for gait in the lumbar spinal cord, this is possible in the cat with a transected thoracic or cervical cord. Such an injured cat will step if supported upon a moving treadmill and given drugs, such as dopamine receptor agonists, that facilitate motor excitability. In theory, humans should be able to do this as well. However, there are few reports of people with spinal cord injuries losing the ability to walk and then recovering spontaneous ambulation.

As people age, muscle strength decreases by up to 25%. In addition, older people have a compromised sense of balance, in part due to senile otocional degeneration and a declining ability to maintain posture. These changes result in a more conservative gait characterized by:

- More time spent in double support
- Reduction in stride length
- Reduction in speed

Even in athletic people of advanced age, the amount of walking time in double support increases and the amount of running time spent airborne decreases. Older people tend to walk with less agility, bending their ankles less, extending their hips less, and swinging their arms less. In general, the safety factor for walking decreases in the elderly. For instance, an older person runs a high risk of tripping and falling because the clearance between the foot and ground during the swing phase decreases.

Deterioration in vision further exacerbates this risk. Finally, the psychological impact of fear should not be underestimated as the elderly may have either fallen themselves or watched a loved one fall, learning firsthand the difficult struggle required to recover from such an event. Along with physical and neurological deterioration, fear of falling leads people to overcompensate by, for example, widening their stance, which unfortunately increases, rather than decreases the chance of falling.

PERIPHERAL FEEDBACK REINFORCES GAIT AND ADJUSTS LOCOMOTION TO EXTERNAL CONDITIONS

Remember that central pattern generators produce a baseline movement and do not require any peripheral, sensory feedback or reflex participation to do so. Although true, this principle is a somewhat artificial construct as the movement produced by a deafferentated central pattern generator will only work under ideal circumstances (i.e., when a person in the peak of health and load-free walks across a flat, hard surface). Even in these idealized circumstances, the movement provided by a central pattern generator alone would be clearly “off,” not quite normal. On the other hand, when a middle-aged professor, with the beginnings of arthritis, carrying a briefcase in one hand and a gym bag in the other, cuts across a rain-slick football field, sensory feedback is absolutely critical to reinforce and modify the core movements involved in gait and thereby prevent stumbling.

An example of sensory feedback, from Ia afferents, reinforcing the basic movements involved in gait occurs when the leg is extended behind the body and about to lift off. Leg extension, caused by contraction of hip extensors, stretches hip flexors such as the iliopsoas and quadriceps muscles (see Box 22-9). This stretch excites Ia afferents that in turn excite the homonymous muscles—the iliopsoas and quadriceps—facilitating hip flexion and lifting the foot off the ground. In this example, *extending the leg backward passively stretches the relaxed hip flexors, triggering a stretch reflex that in turn helps lift the leg to start the swing phase* (Fig. 22-8A-B).

In a second example of sensory feedback, feedback from Ib afferents reinforces the fundamentals of gait and ensures that muscle strength matches load. Consider a person carrying a toddler in one arm and groceries in the other. The combined weight of the loads is opposed by strong contractions of leg extensors acting at the knee and ankle, the quadriceps and gastrocnemius muscles, respectively. Recall that the quadriceps serves as both a hip flexor, as in the first example, and a knee extensor, as in this example. The strong contractions of the quadriceps and gastrocnemius muscles excite Ib afferents—and here a funny

Box 22-9

THE PROPULSION COMPONENT OF WALKING STRETCHES HIP FLEXORS.

If you recall that Ia afferents sense passive stretch, it may be surprising that the active extension of the leg during locomotion excites Ia afferents. The solution to the paradox is that the active muscles are hip extensors and that the *contraction of the hip extensors produces a passive stretch of the hip flexors*. Thus, passive stretch can result from an external load or from the active contraction of antagonist muscles, as in this case.

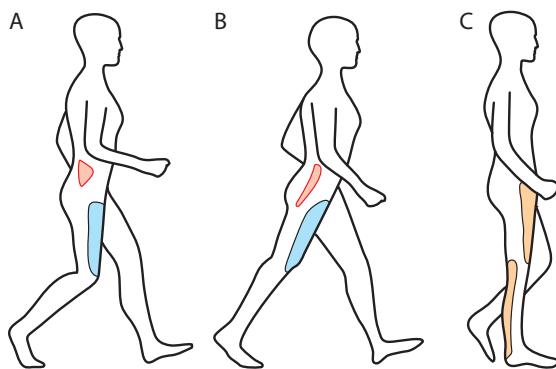


Figure 22-8. A–B: Feedback from Ia afferents innervating the iliopsoas (red) and quadriceps (blue) muscles signals the stretch caused by hip extensors and excites the homonymous muscles contributing to the hip flexion needed for lift off. In A, both muscles are short and neither is stretched. When the leg extends back (B), extending the hip joint, both muscles are stretched. Stretching these muscles facilitates the hip flexion needed for take off. C: During stance, the quadriceps (upper tan) and gastrocnemius (lower tan) muscles contract to bear the weight of the body and load. The stronger the contraction, the more excitation of Ib afferents occurs. During locomotion, Ib activation leads to *excitation* of the homonymous muscles disinaptically. Note that the excitatory effect of Ib afferents on the homonymous muscle only occurs during locomotion and is exactly opposite to the effect mediated by the Ib reflex at other times.

thing happens. Instead of inhibiting the homonymous muscles, the effect of Ib afferents is reversed—*during locomotion*—to excite them (Fig. 22-8C). The *excitation of leg extensors prolongs the stance, ensuring that the leg does not take off until the other leg has accepted enough weight*. Thus, this reflex guarantees that a person's leg will not buckle while walking with a heavy load. In people with weakened muscles, the body itself may be sufficiently heavy to elicit a prolongation of the stance phase, resulting in a delay in lift off and a general slowing of gait.

Unexpected external objects elicit rapid reflex reactions, rapid enough to allow people to recover from a stumble or slip without actually falling and to do so with time to spare. In fact, *healthy people rarely trip or fall, largely because the stumbling correction reaction is excessively fast and highly redundant*. Many things have to go wrong before the system fails, a feature commonly referred to as a large “safety factor.”



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CHAPTER 23

FROM MOVEMENT TO ACTION: POSTURAL STABILITY, ORIENTING AND PRAXIS

Isolated from the brain, the spinal cord does not generate recognizable movements. Even the knee jerk reflex looks very different in a person with a complete spinal transection than in a healthy individual. How could this be if the stretch reflex only requires intact Ia afferents and motoneurons, neither of which are damaged by a spinal transection? The reason is simple: all spinal functions degrade when the spinal cord operates in isolation. Although the absolutely essential circuit for the stretch reflex consists of only two neurons, the reflex circuit receives thousands of synaptic inputs from other neurons and does not work normally in the absence of this input. To produce smooth coordinated movements, all parts of the nervous system, spinal cord included, must function within the context of the whole, intact nervous system. Yet, because the student cannot learn the motor workings of the entire nervous system in one sitting, we divvy up this complexity using anatomical distinctions as our guide. In this chapter, we examine how motor control centers in the brainstem and forebrain influence the activity of motoneurons in the spinal cord and brainstem, taking us one step closer to a more integrated and realistic picture of how we move.

MOTOR CONTROL CENTERS MAINTAIN POSTURE AND GENERATE PURPOSEFUL MOVEMENTS

When all motor control centers that influence motoneurons are in working order, we move as normally as the condition of our body permits. The failure of one motor control center will severely impact some movements, slightly impact others, and only subtly change still others. In this chapter, we concentrate on the core functions of the most important motor control centers and their tracts. Thus, the role of the vestibulospinal tract in postural control

is emphasized even though the vestibulospinal tract also plays important roles in orienting, reaching and many other types of movements. The student should understand that this teaching strategy hits the highlights of motor control function without being either complete or error-free.

Regions in the brainstem and forebrain comprise the higher levels of the motor hierarchy that direct motoneuronal activity, participating in the full complement of movements that humans and other mammals can make. This chapter details how neurons in motor control centers initiate movements that fall into three categories:

- **Postural stability** means maintaining the preferred position of the body during self-generated movements and against unexpected perturbations.
- **Orienting movements** refer to movements that turn a person's body and gaze toward a sensory stimulus, such as a moving target, unexpected sound, or unpleasant odor, or toward a remembered place in space as occurs when you look up, anticipating a friend's approach. In this chapter, we briefly consider the mechanisms used to move the body but leave our discussion of gaze to Chapter 26.
- **Voluntary action or praxis** includes speech, facial expressions, reaching, grabbing, holding, playing the piano, and so on.

Neurons in motor control centers located in the brainstem and cerebral cortex influence movement through descending tracts that reach the spinal ventral horn and motor cranial nerve nuclei to contact motoneurons and motor interneurons. As you recall from Chapter 9, motoneurons located in the medial portion of the ventral horn innervate axial muscles and more laterally located motoneurons innervate progressively more distal limb muscles. It should not be surprising then that *the major descending tracts that influence motoneuron activity can be divided into medial tracts that control posture and orientation through effects on the axial and proximal limb musculature and lateral tracts that mostly control the movements of the hands, feet, and face* (Fig. 23-1):

- Medial tracts for posture:
 - Lateral vestibulospinal tract
 - Reticulospinal tracts
 - Anterior corticospinal tract
- Medial tracts for orientation and gaze control:
 - Medial vestibulospinal tract
 - Tectospinal tract
- Lateral tracts for control of appendicular and face musculature:
 - Lateral corticospinal tract
 - Corticobulbar tract
 - Rubrospinal tract

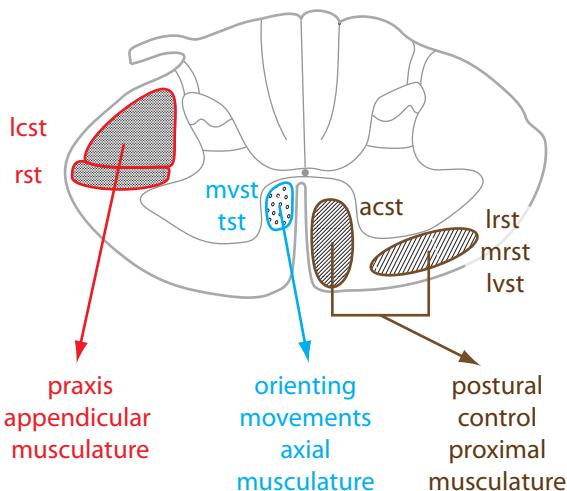
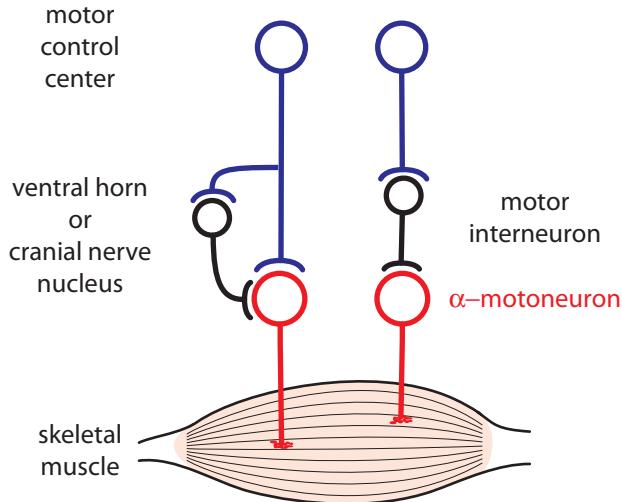


Figure 23-1. The tracts that mediate orienting movements and postural control lie medial to those responsible for voluntary movements of the distal musculature. The corticobulbar tract terminates in the caudal medulla and therefore is not present in this section through the cervical enlargement. The lateral corticospinal (*lcst*) and rubrospinal (*rst*) tracts are the primary tracts used for voluntary praxis using appendicular or limb muscles. The corticobulbar tract (not present here) is used for voluntary praxis using facial, oral and upper airway musculature. Orienting movements of the body are coordinated primarily by the medial vestibulospinal (*mvst*) and tectospinal (*tst*) tracts. The tectospinal tract runs the length of the spinal cord and reaches motor circuits controlling proximal leg and trunk movements. In contrast, the medial vestibulospinal tract ends at cervical levels and primarily influences shoulder and neck movements. The medial longitudinal fasciculus (not present here) runs the length of the brainstem and coordinates eye movements important for orienting movements. The anterior corticospinal (*acst*), reticulospinal (lateral, *lrst*; and medial, *mrst*) and lateral vestibulospinal tracts are the primary tracts used for ensuring postural stability. Proximal musculature both in the trunk and limbs is used for most postural adjustments.

The nervous system makes a further distinction between simple, often bilaterally symmetric, movements that employ axial and proximal muscles—standing up from a chair, waving hello, taking a bow—and complex, fractionated movements that require distal muscles—opening a latch, playing the piano, writing, playing a game of paper-rock-scissors. Although axial and appendicular are not useful terms with respect to facial, tongue, and upper airway musculature, the distinct brain circuits support simple movements—raising both eyebrows, frowning, opening one's mouth, sticking out one's tongue, humming—and more complex movements such as dislodging a piece of food from between two teeth, raising one eyebrow to convey disbelief, or speech.

All descending tracts, medial and lateral, contribute to simple or axial movements, but only the corticospinal and corticobulbar tracts support complex, fractionated movements. Indirect projections from motor control centers to motoneurons, via motor interneurons, are sufficient to produce simple, bilaterally symmetric movements (Fig. 23-2). In contrast, complex, fractionated movements arise, at least in part, from direct projections from motor control centers to motoneurons (Fig. 23-2). Because numerous indirect projections arise and travel separately from the direct portion of the corticospinal and corticobulbar tracts, impairment of complex fractionated movement is often not accompanied by deficits in movements supported by indirect projections. Therefore, many patients with a motor cortex injury that prevents them from dancing the jig or playing the guitar still walk, sit down, stand up, reach out, and even pick up objects, albeit awkwardly (see Box 23-1).

Figure 23-2. Neurons in motor control centers (blue) project to motor interneurons (black), motoneurons (red), or both. Pathways with at least some direct projections to motoneurons support fine fractionated movements of the distal limbs and lower face. Projections from motor control centers to interneurons including neurons that participate in central pattern generator circuits support axial, proximal, and bilaterally symmetrical movements.



THE GOAL OF POSTURAL CONTROL IS TO KEEP THE CENTER OF FORCE DIRECTLY ABOVE THE SUPPORT SURFACE

Humans adopt a number of *postures* or body positions and maintain them against gravity and other forces by the neural process of *postural control* or *balance*. The difficulty of holding a given posture depends on two factors:

- *The center of mass*: this is relatively high for an upright human, located at a spot about 55%–60% of one's height, typically just below the belly button.
- *Support surface*: points where the body contacts the ground define the outer edge of the support surface. For a human standing on flat feet this region—between and including the feet—is relatively small (compared to a quadruped like a cat), and for someone on tip toes even smaller.

Postural stability is a marvel, unparalleled by any existing artificial circuit. Given a comparable physical starting point to that of humans (similarly high center of mass and small support surface area), no robot, no matter how advanced, could remain upright while riding a city bus (see Box 23-2). Further, postural control circuits contain so many safeguards that quite a bit of damage to the system can be tolerated, enabling humans to stand even in their advanced years, after a lifetime of accumulated insults.

The ease of maintaining balance depends on the size of the support surface, which in turn depends on posture in a straightforward way:

- When *lying prone*, the support surface is at a maximum and postural control is easy.
- When *sitting*, the support surface is intermediate in area and postural control is of intermediate difficulty.

LESIONS OF DESCENDING MOTOR TRACTS AND OF MOTONEURONS PRODUCE DIFFERENT SETS OF SYMPTOMS.

Descending motor tracts influence but do not completely control the activity of motoneurons. Illustrative of the type of influence exerted by descending tracts upon motoneurons is a comparison of the effects of lesions to descending motor tracts and motoneuron lesions. As the reader knows, there is no possibility for movement after motoneurons are damaged. Thus, when a motoneuron disease like poliomyelitis kills motoneurons, no active movements, not even reflexes, are possible using the denervated muscle. In contrast, when descending motor tracts are lesioned, for example after spinal cord transection or a middle cerebral artery stroke, *hyperreflexia*, a condition of enhanced reflexes, accompanies the inability to make volitional movements.

The areflexia resulting from motoneuron death and the hyperreflexia that accompanies descending motor tract damage have further consequences (see Table 23-1). Areflexive muscles lose tone and become *atrophied* from disuse. Muscle fibers that are not innervated by a motoneuron show spontaneous contractions of entire motor units, fasciculations, and of single muscle fibers, fibrillations (see Chapter 21). In contrast, stretch reflexes are large in magnitude and occur *briskly* in hyperreflexive individuals. Muscle tone is often elevated. Hyperreflexia and the consequent increase in muscle tone mitigate the muscle atrophy that would normally result from disuse of a muscle due to an inability to willfully use that muscle. There are no consistent electromyographic (EMG) signs of damage to descending motor tracts, although transient signs of denervation may occur.

It is not clear which of the descending motor tracts is most critical to reflex inhibition. Lesions both within and outside of the corticospinal tract appear to contribute. Many diseases only affect motoneurons, or only affect descending motor tracts, but some affect both. One example of the latter is **amyotrophic lateral sclerosis**. Patients with amyotrophic lateral sclerosis typically seek medical help because of muscle weakness exhibited as dysarthria, dysphagia, clumsiness, or foot drop. When first seen, these patients typically present with signs of damage to descending tracts—muscle weakness, hyperreflexia, and increased muscle tone—as well as signs of motoneuron damage—muscle atrophy, fibrillations, and fasciculations. The involvement of both motoneurons and descending tracts reflects the suspected pathophysiology of amyotrophic lateral sclerosis, in which connected pairs of corticospinal tract neurons and motoneurons both degenerate. Unfortunately, amyotrophic lateral sclerosis is fatal, usually within a year or two, and no treatment currently exists. Ultimately, patients with amyotrophic lateral sclerosis lose mobility and become wheelchair-bound. Fatal complications include weakness in swallowing, potentially causing insufficient nutrition or aspiration of food, and weakness in respiratory muscles.

In sum, reduced reflexes indicate a problem at the level of the motoneuron, and brisk reflexes signal damage to descending motor tracts. Only a few specific diseases, such as amyotrophic lateral sclerosis, involve signs of damage to both motoneurons and descending motor tracts. Therefore, reflex testing is invaluable in rapidly narrowing down the diagnostic possibilities in a patient with a motor disorder.

- The *bipedal upright* position utilizes a limited support surface, and consequently, is challenging to maintain, even more so with a narrow than with a broad stance.

To avoid toppling over, the center of mass of a *passive* body must lie above a point within the support surface, the area within which the body contacts the ground (Fig. 23-4A). Recall from Newtonian physics that:

$$\text{Force} = \text{mass} * \text{acceleration}$$

TABLE 23-1. THE SYMPTOMS ASSOCIATED WITH LESIONS OF MOTONEURONS, THEIR AXONS, OR THE NEUROMUSCULAR JUNCTION ARE DIFFERENT FROM THE SYMPTOMS ASSOCIATED WITH LESIONS IN DESCENDING MOTOR TRACTS

	MOTONEURON LESION	LESION OF DESCENDING TRACTS INCLUDING CORTICOSPINAL TRACT
Volitional movement	Weak or none	None; paralyzed (if corticospinal tract is involved)
Reflexive movement	Hyporeflexia or areflexia	Hyperreflexia
Muscle tone	Decreased or absent	Increased
Muscle appearance	Moderate to severe atrophy from disuse	Mild atrophy from disuse mitigated by the hyperreflexive use
EMG findings suggestive of muscle denervation	Fibrillations, fasciculations	Typically transient if present

From this equation, we realize that: (1) for an active, moving body, it is the **center of force** that must lie over the support surface; and (2) that two basic types of disturbances can impact the center of force:

- **Mass:** Imagine picking up an infant at arm's length. Without postural adjustments, you would fall forward.
- **Acceleration:** Imagine throwing a punch or being punched. Without compensatory postural adjustments, the body would topple in the direction of the acceleration, or in other words, with the punch.

Box 23-2

BALANCE ON TWO LEGS WITH A HIGH CENTER OF GRAVITY IS DIFFICULT.

Since the landing of the Mars *Pathfinder* in 1997, a series of robotic, all-terrain vehicles have roamed, for increasingly long journeys, over Mars' surface. Designers of these Mars rovers were so concerned about balance that they gave the rovers six wheels and placed the center of mass very low, allowing the vehicles to remain upright even at tilts up to 45 degrees. Even so, the 2005 version, the *Opportunity*, traveled at an average speed of 118 feet (or 36 meters) per hour, more than 130 times slower than a moderate walking speed. At one point, the *Opportunity* spun its wheels forward and backward for nearly 5 weeks, trying to step over a 20 cm-high "hill." This story highlights the trade-off between postural stability and locomotion. The *Opportunity*, with its low center of mass and wide support surface, stays upright but advances slowly, like a turtle,

and with difficulty. In contrast, upright humans, with their high center of mass and small support surface, can achieve much faster speeds than those achieved by the bottom-heavy, "sextupedal" Mars rovers but must employ complex brain circuits to maintain balance.

Recently, Boston Dynamics has produced a remarkable robot, named PETMAN, that walks bipedally at different speeds and remains upright even when pushed. This extraordinary achievement was made possible by programming gait, proprioceptive, and vestibular systems into the robot that resemble those present in us (Fig. 23-3). So, with a great deal of money and the efforts of many talented engineers and scientists, it is possible to *nearly* match the performance of the human brain and body that we are all born with.

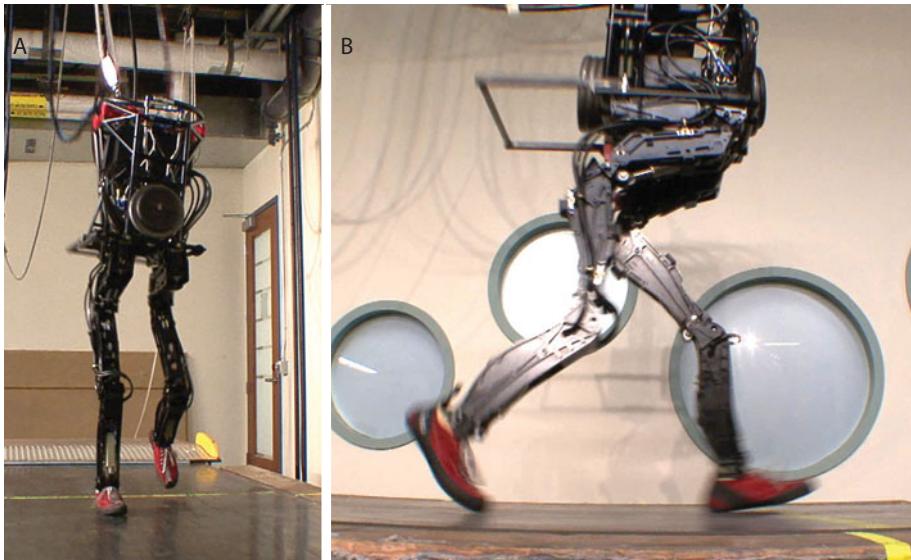
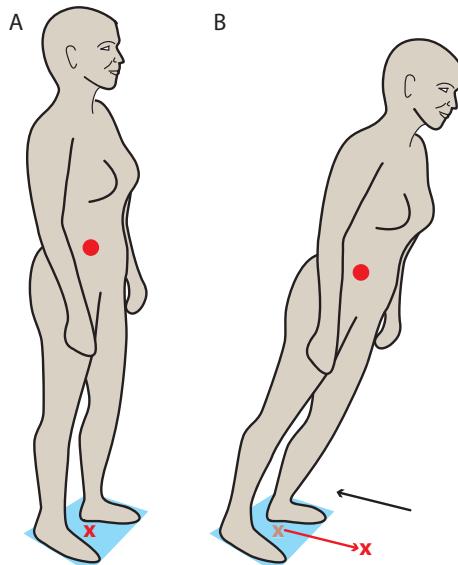


Figure 23-3. PETMAN is a robot with a bipedal gait modeled after our own. PETMAN has ankle-, knee-, and hip-like joints and walks using a typically human swing and stance gait. PETMAN was designed to walk with the heel striking the ground first and the toe leaving the ground last (B). PETMAN images courtesy of Boston Dynamics ©2010.

To oppose disturbances of mass or acceleration and move the center of force back to a spot overlying the support surface, we use muscular force. A myriad of abdominal muscle-strengthening exercises use exactly this principle by requiring force from the abdominal musculature to maintain balance when the body's center of mass does not lie above the support surface. When holding an infant at arms' length, isometric contractions of the gastrocnemius and paraspinous muscles provide a force in the backward direction to oppose the forward shift in center of force that would occur in the absence of any muscular effort. The farther that the center of mass shifts from a point above the support surface, the more force required to oppose the shift and maintain balance. Only very strong, well-practiced gymnasts, dancers, and body contortionists can keep a steady posture in which the center of mass lies far outside the support surface (Fig. 23-4B).

Figure 23-4. When standing, the center of mass (red dot) for an average human is just below the belly button. A: Postural stability is easiest if the center of mass lies above the support surface (red x in blue shape). B: Leaning forward displaces the center of mass (red arrow) to a point in front of the support surface. Maintaining stability for a posture in which the center of mass is outside of the support surface requires muscle force (black arrow) that opposes the displacement of the center of mass.



ANTICIPATORY ADJUSTMENTS MAINTAIN POSTURE DURING STANDING AND OTHER CONDITIONS OF SELF-MOTION

Standing still is an illusion. Since the late 19th century, we have known that “standing still” involves continuous adjustments, albeit small ones, which generate an oscillatory sway. This sway increases with age. Bipedal human standing relies in great part upon the elastic properties and stability of the ankle structure and requires minimal, tonic muscle activity from soleus muscles and virtually none from thigh muscles, including the quadriceps. What is remarkable about reflexes during human standing is that they are primarily feed-forward or anticipatory rather than feedback in nature. This means that with each activation of the soleus muscle, reflex sensitivities are adjusted to minimize the potential disturbance produced by the ensuing soleus action. In other words, *perturbations to balance are prevented before they happen rather than being corrected after they have occurred.*

All self-generated actions, not just standing, elicit anticipatory movements that prevent postural instability before it happens. To convince yourself of this, take this textbook (mark your place first) in your right hand and raise it to the right. Then stand with your left shoulder and side next to a wall. If you now try to perform the same action, you will fall over, to the right, toward the location of the shifted center of mass. This is because the postural shift made “unconsciously” prior to lifting the textbook was prevented by your proximity to the wall. As another example, when standing up from a seated position, people visibly move their center of mass forward before propelling themselves upward (Fig. 23-5). More subtle postural adjustments accompany all self-generated movements, even those made from a supine position.

During all self-motion—kneeling down, carrying an infant, running, reaching—the center of mass moves rapidly in varied directions, and postural adjustments prevent falling from happening. Postural adjustments, visible or subtle, anticipate, and prevent any loss of balance before it even has a chance to occur. Although postural

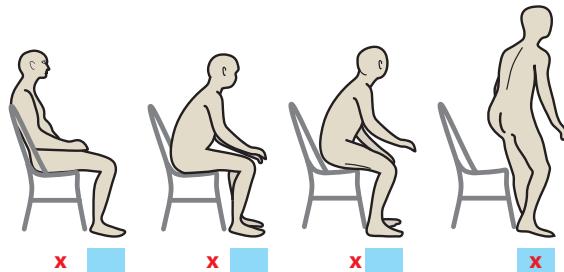


Figure 23-5. In preparation for rising from a sitting position, people lean forward to advance their center of mass before rising. Leaning forward is absolutely necessary, as you will learn if you try to rise straight up from a seated position. In this cartoon of a man rising from a chair, the projection of the body's center of mass is marked by a red x. The position of the support surface after standing is marked by a blue rectangle. Note that in the seated position, the support surface includes the region of contact between the body and the chair. To rise from a sitting position, the center of mass is first advanced by leaning forward. Yet, even leaning forward does not place the center of mass within the standing support surface. To move the center of force over the support surface, force from the contraction of leg muscles shifts the center of force both forward and up.

Modified from Muybridge, Eadweard. *The human figure in motion: An electro-photographic investigation of consecutive phases of muscular actions.* London: Chapman & Hall, 1904.

adjustments can precede a primary, intended movement, the order of the primary and postural activations is less important than the fact that *postural adjustments occur in the absence of any actual postural perturbation, precluding any disturbance of equilibrium before it happens*. Thus, postural control circuits *anticipate* potential disturbances to equilibrium that our intentional movements would cause if uncorrected and thereby prevent the occurrence of such disturbances.

A great deal of brain power is devoted to postural stability. In addition, as described in Chapter 22, unexpected perturbations of muscle elicit reflexive adjustments with a high safety factor. These measures are designed to make postural balance fail-safe. In fact, *healthy people do not fall normally, certainly not during everyday activities such as standing and walking*. Therefore, a person falling, in the absence of an obvious cause such as an icy or slick surface, typically signifies a problem.

FEEDBACK REFLEXES CONTRIBUTE TO POSTURAL CONTROL IN UNPREDICTABLE ENVIRONMENTS

Challenges to balance occur when people stand in unpredictable environments, such as on a boat in stormy seas or in a bus in stop-and-go traffic, and when people balance on a small support surface, such as a narrow beam or tree limb. Somatosensory afferents detect and signal unexpected forces that impact the center of mass and elicit *feedback* corrections from descending postural motor tracts. Basic motor reflexes provide rapid, appropriately sized, and effective adjustments to *unanticipated* perturbations. Visual input—“Gee everything looks tilted”—can also initiate postural adjustments. Finally, vestibular input makes a critical contribution to postural stability. *In terms of postural control, falling rapidly excites lateral vestibulospinal tract neurons that increase physiological extensor activity, opposing gravity and promoting an upright posture.* The lateral vestibulospinal tract descends ipsilaterally from the lateral vestibular nucleus for the entire length of the spinal cord.

DESCENDING POSTURAL TRACTS GENERATE ADJUSTMENTS USING A VARIETY OF MECHANISMS

The descending motor tracts most closely concerned with posture—lateral vestibulospinal, reticulospinal and anterior corticospinal tracts—contribute to both feedback and anticipatory postural adjustments. For anticipatory postural adjustments, the command initiating an action is *copied* to one or more of the descending postural tracts, which in turn contact motor interneurons. In addition, the lateral vestibulospinal and reticulospinal tracts terminate on γ -motoneurons. Recall from Chapter 22 that activation of γ -motoneurons excites α -motoneurons via the γ -loop (excitation of γ -motoneurons \rightarrow contraction of polar regions of intrafusal fibers \rightarrow stretch of intrafusal fiber equator \rightarrow excitation of Ia afferents \rightarrow excitation

of α -motoneurons → muscle contraction). Thus, descending postural tracts influence muscle activation at least in part through an indirect mechanism that depends on sensory input from spindle afferents.

Although top-down connections routed through the descending postural tracts are clearly needed for the adjustments that occur in concert with self-generated movements, descending postural tracts also play a role in *feedback* postural reactions by modifying the sensitivity of corrective reflexes. The reversal of the Ib reflex from inhibition to excitation during locomotion is one example of **reflex modulation**. Another example is the increased sensitivity of the Ia reflex during situations of equilibrium instability, such as walking on a narrow beam. Projections from descending tract neurons to γ -motoneurons and motor interneurons modify the sensitivity of basic spinal motor reflexes. In this way, *descending postural tracts provide a central control system that regulates the center of force and also adjusts reflex sensitivities, even reversing the output of a reflex, to stabilize posture and maintain balance during self-generated movements*. If descending postural tracts are interrupted, an abnormal posture results (see Box 23-3).

Box 23-3

LESIONS IN DESCENDING POSTURAL TRACTS PRODUCE ABNORMAL TONIC POSTURES.

Lesions that sever forebrain inputs from descending motor tracts result in abnormal postures. With a midbrain lesion, people lie in a **decorticate posture**, whereas more caudal lesions, in the pons, cause a **decerebrate posture**. The decorticate posture is marked by foot and leg extension along with arm flexion and adduction. The decerebrate posture includes extension of both arms and legs. Both postures reflect unchecked activity in postural control tracts. For example, during decerebrate posturing, medullary reticulospinal and lateral vestibulospinal tract cells elicit extensor activity but are unopposed by damaged pontine reticulospinal tract cells that would normally activate flexors. Both decorticate and decerebrate postures signal brainstem damage and thus a medical emergency.

ORIENTING MOVEMENTS LARGELY DEPEND UPON THE TECTOSPINAL TRACT

The superior colliculus is a phylogenetically conserved structure that serves as the only visual processing center in vertebrates such as amphibians and reptiles who lack an expansive cerebral cortex. In visual animals such as humans, the superior colliculus receives primarily retinal input but also receives auditory and somatosensory input. The superior colliculus integrates all of this sensory information to locate stimuli in the world. The superior colliculus efficiently locates visual stimuli that change across time (fluttering) or space (actually moving), but is “blind” to both form and color. The superior colliculus transforms sensory input into a motor map, a process termed **sensory-motor transformation**. The motor signal emerges from the middle layers of the superior colliculus and travels contralaterally through the *tectospinal tract* to contact interneurons and central pattern generators in the brainstem and cervical spinal cord. The result of superior colliculus activity is an orienting movement of the shoulders, neck, and eyes toward a stimulus on the opposite side.

PRAXIS FORMS THE CONNECTION BETWEEN THE BRAIN AND THE OUTSIDE WORLD

The inability to effect one’s internal ideas upon the physical world produces great suffering in locked-in patients such as Jean-Dominique Bauby, introduced in the first chapter. This inability stems from a loss of **praxis**.

Praxis refers to the physical actions that arise from cognitive processes, including internal thoughts and perceptions of external events. Three main pathways connect the internal thoughts and processes of the forebrain to movement-producing circuits in the brainstem and spinal cord:

- Cortical neurons engage neurons of the *rubrospinal tract* for fundamental movements of the body such as walking, reaching, or grasping but not for fine movements such as berry-picking or typing.
- Volitional movements of the skeletal muscles in the neck, body, and limbs—particularly fine motor acts—depend on the *lateral corticospinal tract*.
- Volitional movement of the skeletal muscles in the oral cavity, larynx, and face, such as are required for eating, winking, and speech, depend on the *corticobulbar tract*.

As you recall from Section 3 on Neuroanatomy, the lateral corticospinal tract and parts of the corticobulbar tract travel through the pyramids at the base of the medulla. Additional descending pathways, including the rubrospinal tract, also contribute to motor control but since they travel outside of the pyramids, these additional tracts are often called **extrapyramidal** (see Box 23-4).

THE RUBROSPINAL TRACT SUPPORTS POSTURE, LOCOMOTION, AND REACHING

The rubrospinal tract arises from neurons in the red nucleus (see Chapter 12). Large-celled, or magnocellular, red nuclear neurons give rise to the rubrospinal tract. Their axons immediately cross the midline, within the midbrain at the level of the red nucleus, and travel down into the spinal cord, just ventrolateral to the

Box 23-4

EXTRAPYRAMIDAL IS A CATCH-ALL TERM FOR DIVERSE MOTOR PATHWAYS.

The term *extrapyramidal* refers to a varied group of motor tracts that travel separately from corticobulbar and corticospinal tracts. Extrapyramidal pathways arise from diverse cortical and subcortical areas, travel heterogeneous routes, and generate movements that are automatic, subconscious, or emotional rather than deliberate. The term is essentially a term of exclusion and as such refers to a

catch-all category of motor pathways. Despite its lack of specificity, the term is useful in referring to pathways that produce nondeliberate, self-generated movements. As the patients illustrated in Figures 20-2 and 20-3 demonstrate, these pathways certainly exist. A better understanding of the trajectories traveled by extrapyramidal tracts is an important area for future investigation.

lateral corticospinal tract (Fig. 23-1). Although its precise function in humans is unclear, the rubrospinal tract is *the* motor command center in lower vertebrates that lack a well-developed motor cortex. Patients with lesions of the motor cortex who cannot, for example, lift their leg in response to a verbal command can still stand and walk, admittedly awkwardly, probably in large part due to their intact rubrospinal tract. Similarly, *patients with a compromised lateral corticospinal tract can still reach and point under certain circumstances, residual functions that likely employ an intact rubrospinal tract.*

FINE VOLUNTARY MOVEMENTS OF THE BODY, ORAL CAVITY, AND FACE DEPEND UPON THE LATERAL CORTICOSPINAL AND CORTICOBULBAR TRACTS

We exert exquisitely fine control over our facial, oral, and distal appendicular muscles using corticobulbar and corticospinal tracts. Consider how many English consonant sounds require that the tip of the tongue touch the anterior pole of the palate—d, l, n, t. Although very few of us could describe the fine differences in muscle usage that allow us to say “ta” in place of “da” or vice versa, virtually all who grew up speaking English encounter no difficulty in producing these two sounds when desired. Just as speech and “making a scary face” depend on the corticobulbar tract, shuffling cards, dicing vegetables, and braiding hair depend on the lateral corticospinal tract. The basis pontis and the cerebellar hemispheres, both disproportionately expanded in primates, especially humans, relative to rodents for example, coordinate with the motor tracts descending from cortex to fine-tune and initiate articulated movements.

Despite the reader’s familiarity with the course traversed by the corticospinal and corticobulbar tracts, these pathways merit further review, with added details regarding somatotopy, due to their importance to human motor function. The corticospinal and corticobulbar tracts arise from neurons in a wide cortical distribution, including primary motor cortex, somatosensory areas of parietal cortex, premotor cortex, and the supplementary motor area. They target primarily interneurons as well as some motoneurons in the spinal cord and cranial nerve nuclei.

Each of the cortical regions contributing to descending motor tracts is somatotopically organized. Primary motor cortex exhibits a striking somatotopy, with very large regions of cortex devoted to certain small parts of the body such as the lips and small areas of cortex concerned with large body sections such as the trunk (see Fig. 13-10). *The relative cortical area controlling different body parts is related to the precision with which movements of the regulated muscles are controlled.* Beyond the gross topography from medial (toes) to lateral (face), organization of the primary motor cortex is rough, with the same muscle controlled by cells in nonadjoining cortical regions, and neighboring regions of cortex controlling muscles located at some distance from each other. Also recall that the extraocular muscles are not represented in primary motor cortex but are controlled by a separate motor control area—the frontal eye fields.

Corticospinal and corticobulbar axons descend from cortex through the corona radiata and into the internal capsule, where the face is represented in the genu and the arms, trunk, and leg in progressively more caudal regions of the posterior limb. The internal capsule continues caudally to form the middle third of the midbrain cerebral peduncles. Within the cerebral peduncles, corticobulbar fibers travel medially to corticospinal fibers with arm-, trunk-, and leg-controlling fibers coursing in progressively more lateral locations, all within the middle third of the peduncles. The peduncles feed into the base of the pons, where corticospinal and corticobulbar tract axons travel in bundles, interspersed like islands within a sea formed by the pontine nuclei. In the pons, the somatotopy is roughly similar, but far cruder, to that present in the cerebral peduncles, with face represented most medially and legs most laterally. Upon entering the medulla, fibers descending from cortex coalesce within the pyramids, where the somatotopy shifts slightly so that the remaining face-controlling axons lie dorsomedially and leg-controlling axons lie most ventrolaterally.

At the spinomedullary junction, virtually none of the corticobulbar tract remains. The only exception is axons destined for the spinal accessory nucleus within the most rostral cervical spinal segments. At this point, 90% of the corticospinal tract fibers decussate to descend within the dorsal part of the lateral funiculus, contralateral to the motor cortex where they originated, as the lateral corticospinal tract. *Thus, voluntary control of muscles on one side depends on neurons in the motor cortex on the other, contralateral, side. Remember that within the forebrain and brainstem, lateral corticospinal input travels contralaterally to the muscles that it ultimately controls. However, within the spinal cord, lateral corticospinal input courses on the same side as the muscles that it controls.* The 10% of the corticospinal tract that fails to decussate descends ipsilaterally within the anterior corticospinal tract, which serves primarily to stabilize posture during voluntary movements and to voluntarily control axial movements.

THE CORTICOBULBAR TRACT CONTROLS SOME MOVEMENTS IPSILATERALLY, OTHERS CONTRALATERALLY, AND STILL OTHERS BILATERALLY

As they descend through the brainstem, corticobulbar tract axons terminate at the:

- Motor trigeminal nucleus to control muscles needed for chewing
- Facial nucleus to control muscles of facial expression
- Nucleus ambiguus to control laryngeal and other upper airway muscles
- Spinal accessory nucleus to control muscles used for shrugging the shoulders and turning the head
- Hypoglossal nucleus to control tongue muscles

Although the spinal accessory nucleus is in the spinal cord and not the brainstem, it is convenient to categorize descending projections from cortex to the spinal accessory nucleus as part of the corticobulbar tract. The corticobulbar tract resembles the lateral corticospinal tract in virtually every feature *except* that it does not always control motoneurons and movements contralateral to the side of origin. Consistent with the variation in terminal laterality, unilateral corticobulbar dysfunction produces variable clinical signs across the different cranial nerve nuclei:

- *Motor trigeminal*: no discernible deficit as the muscles of mastication receive bilateral inputs
- *Facial nucleus*: loss of expressions in the contralateral lower face (see more below)
- *Nucleus ambiguus*: deficits in swallowing, termed dysphagia, or articulation, dysarthria, and the like due to the necessity of bilateral muscle coordination in the movements involved
- *Spinal accessory nucleus*: due to a largely ipsilateral projection, there is weakness in shrugging the ipsilateral shoulder and rotating the head to look contralaterally
- *Hypoglossal nucleus*: largely contralateral loss that results in the tongue sticking out toward the sign of the lesion

CORTICOBULBAR INNERVATION OF THE FACIAL NUCLEUS DIRECTLY CONTROLS EXPRESSIONS OF THE BOTTOM HALF OF THE FACE

Corticospinal and corticobulbar tracts share the common function of supporting fine, articulated movements. Here, we focus on the corticobulbar tract's contribution to facial expression in some detail because (1) it is illustrative of how both tracts operate; and (2) deficits in making voluntary facial expressions are clinically important.

Tight control of muscles in the bottom half of the face compared to those in the top half aids humans in eating, a function shared with all other animals, and in speech, a function shared with few other mammals. Only in primates does the corticobulbar tract directly innervate motoneurons that control the muscles of facial expression. In other vertebrates, cortex influences facial motoneurons indirectly via projections to interneurons and central pattern generators in the brainstem reticular core, which in turn project to motoneurons. *Humans retain a pattern of predominantly indirect motor control in the case of the top half of the face*: forehead and eyebrows (frontalis muscle) and eyes (orbicularis oculi). The minor corticobulbar tract innervation of facial motoneurons controlling upper face muscles that exists is mostly bilateral.

You can easily demonstrate to yourself how the direct contralateral pattern of motoneuron control differs from the largely indirect, bilateral pattern in producing

finely controlled movements. Simply compare your ability to make fine, unilateral movements with the top and bottom halves of your face. First, try to contract each buccinator muscle to pull one side of your mouth back (Fig. 23-6A). Then, try to specifically contract each lateral frontalis muscle to raise the eyebrow laterally (Fig. 23-6B). Although almost all readers will be able to individually contract each buccinator muscle, only some readers will be able to raise one eyebrow laterally and even fewer able to raise each eyebrow individually. Furthermore, although no one needed to practice before successfully contracting a buccinator muscle, people typically spend hours looking in a mirror to learn how to raise one eyebrow in isolation.

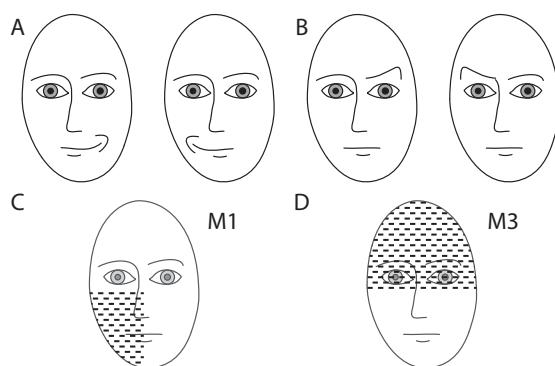
The above exercise illustrates three points:

- Direct projections from motor control centers to motoneurons support the ability to deliberately make fine, fractionated movements.
- Indirect projections from motor control centers to motoneurons support simple bilateral movements.
- Indirect projections from motor control centers to motoneurons may support fine fractionated movements but successful engagement of this pathway requires practice.

Just as a direct connection from motor cortex to motoneurons is not necessary for coarse, often bilateral, facial movements, such a connection is not needed for axial and proximal appendicular movements. Thus, the same type of indirect projection from motor cortex to motoneurons supports coarse body movements.

Since corticobulbar projections innervate primarily motoneurons controlling the lower half of the face (Fig. 23-6C), complete corticobulbar lesions and complete lesions of motoneurons controlling facial muscles will look different. A person with a facial motoneuron lesion, typically involving the facial nerve, cannot move the face on the side of the lesion (see Figs. 10-10 and 23-7). In contrast to the full facial paralysis that results from a motoneuron problem, a **supranuclear**, or above the facial nucleus, lesion of the corticobulbar tract impacts the bottom half of the contralateral face musculature (see Box 23-5). The distinction between supranuclear and motoneuron facial paresis can easily be discerned by asking a person to smile and frown. Someone with a supranuclear facial paresis, cannot lift their mouth on the side opposite to the lesion in a deliberate smile but can frown bilaterally, whereas a patient with a lesion of facial motoneurons can neither frown nor smile on the side of the lesion (Fig. 23-7).

Figure 23-6. Virtually everyone can pull their mouth back to each side (A) but few people can raise each eyebrow laterally (B). C: Primary motor cortex (*M₁*) projects strongly to facial motoneurons that innervate the muscles of the contralateral lower face and does not project directly to facial motoneurons that innervate upper facial muscles. D: The motor area in the anterior cingulate gyrus (*M₃*) projects strongly to facial motoneurons that innervate the muscles of the upper face on both sides.



NERVE AND SUPRANUCLEAR LESIONS PRODUCE DIFFERENT COMPLEMENTS OF SYMPTOMS.

The most common cause of facial motoneuron paralysis is an infection or inflammation of the facial nerve that produces a transient weakness or paralysis termed Bell's palsy. When Bell's palsy affects all branches of the facial nerve, as occurs often, it also produces:

- Hypersensitivity to loud sounds, termed hyperacusis, due to paralysis of the stapedius muscle
- Dry eye and dry mouth, due to lesioning of pre-ganglionic parasympathetic nerves to lacrimal and salivary glands
- Pain radiating from the external ear through effects on the small number of sensory afferents carried in the facial nerve

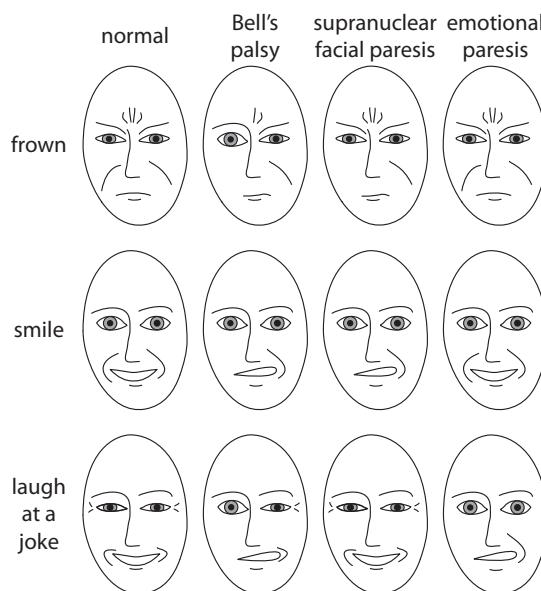
If any of these effects surprises you, you may want to review Chapter 10.

Although numerous symptoms accompany facial paralysis in Bell's palsy, *difficulty in making facial expressions is the only symptom resulting from a supranuclear lesion of fibers destined for the facial nucleus*. This follows from the fact that the corticobulbar tract contains axons from motor cortex involved in controlling facial expression but not axons related to the stapedius muscle, the parasympathetic ganglia, or somatosensation. The difference between a supranuclear lesion and a nerve lesion exemplifies the anatomical cohesion of cranial nerves and the functional unity of central tracts such as the corticobulbar tract.

EMOTIONALLY MOTIVATED MOVEMENTS DO NOT DEPEND ON CORTICOSPINAL AND CORTICOBULBAR PATHWAYS

Regions critical to the generation of voluntary actions are distinct from those needed for the production of emotional actions (see Box 23-6). This concept is best understood and illustrated by comparing the ability of people with

Figure 23-7. Volitional facial expressions (frown, smile) are compared to an emotional facial expression (laugh at a joke) in a healthy adult (normal) and in individuals with Bell's palsy, supranuclear facial paresis, and amimia or emotional paresis. Damage to the facial nerve or facial motoneurons (Bell's palsy) impairs movement of the entire ipsilateral face. Damage to the corticobulbar tract carrying information from M1 to the facial nucleus impairs volitional movements of the bottom half of the face only. The side affected is ipsilateral to the facial nucleus and contralateral to the motor cortex involved. Projections from the anterior cingulate gyrus support emotional movements, so that smiling in response to a joke is preserved in people with corticobulbar lesions. Damage to the pathway from anterior cingulate gyrus to the facial nucleus impairs emotional facial expressions of the contralateral face but not volitional facial expressions.



Box 23-6

WE MAKE A DISTINCTION BETWEEN VOLITIONAL AND EMOTIONAL ACTIONS.

Here, I use the terms *voluntary* and *volitional* to refer to actions that occur in a deliberate fashion, as happens when responding to a verbal command or when play-acting. In contrast, I use the term *emotional* in reference to reactions that occur spontaneously, along with affect and without conscious thought. Recognizing the approximations inherent in these definitions, use of this shorthand is necessary in a neurobiology text that does not double as a philosophical treatise.

different brain lesions to make facial expressions in response to a command or in association with an emotion. For all but the most talented actors, a volitional imitation of an emotional movement differs from the real thing. We easily distinguish a smile of enjoyment from a smile produced in response to a command. A child expertly discerns how angry a parent is by a glance at the parent's facial expression. Patients with lesions in the corticobulbar tract cannot voluntarily make facial expressions but encounter no problem reacting with their face for emotional reasons (see Figs. 20-2, 20-3, and 23-7). In contrast, other patients make facial expressions in response to a command but not in association with an emotion, a condition termed **amimia** (see Box 23-7). Emotional expression is so important to the appearance of a face that a person devoid of expression due to sleep or death can be unrecognizable (see Box 23-8).

How do we understand the dissociation between voluntary and emotional actions? Primary motor and premotor cortices are critical to volitional movements of the face, principally the contralateral bottom half of the face. In contrast, neurons in the *anterior cingulate gyrus*, a part of the limbic system, control emotional facial expressions of the top half of the face (Fig. 23-6D). Many emotional expressions, including fear and pain, depend upon key features in either the top or bottom half of the face and do not require both halves to work in concert, suggesting that facial expressions, like supranuclear pathways, are organized along top-bottom lines (Fig. 13-12). Neurons in the anterior cingulate become active during arousing conditions such as pain, perhaps giving rise to the automatic facial expressions that accompany strongly emotional experiences. The pathway from the anterior cingulate to facial motoneurons does not travel with the corticobulbar tract arising from motor cortex, and thus is extrapyramidal.

Box 23-7

AMIMIA IS A CONDITION OF IMPAIRED EMOTIONAL ACTION.

Patients with **amimia** can act volitionally—smiling for the camera—but cannot act for emotional reasons—smiling when enjoying a funny story (see Fig. 20-3). This rare condition is worth mentioning as it provides insight into how the cortex divvies up different types of movement. Amimia has been reported after lesions in a variety of sites including the frontal cortex, internal capsule, caudate, putamen, and thalamus.

HIGHER MOTOR CORTICAL REGIONS DICTATE ACTIONS RATHER THAN MOVEMENTS

Children playing “Simon Says” stand on one leg, a hungry person stands on tip-toes and reaches for the cookie jar, and we run around obstacles to embrace an old friend arriving after a long absence. Actions have meaning, advancing us toward a goal that is independent of any specific movements or muscles. A child reaching for the cookie jar may use chopsticks to retrieve the jar or may rein in the jar using the hands. Regardless of which movements are used in the quest for a cookie, reaching for the cookie jar is the meaningful deed that constitutes the action.

The myriad of specific reasons that compel people to **act**—move with meaning—fall into three broad categories:

- **Communicative:** People react to verbal requests, as when a person passes the salt shaker to a dining companion or a patient touches her finger to her nose during a medical visit.

Box 23-8

THE UNANIMATED FACE OFTEN BEARS LITTLE RESEMBLANCE TO THE ANIMATED FACE.

In *The Bridge of San Luis Rey*, Thornton Wilder wrote, “Camila had a very beautiful face, or rather a face beautiful save in repose. In repose one was startled to discover that the nose was long and thin, the mouth tired and a little childish, the eyes unsatisfied” This quote eloquently reflects the *active* nature of the facial expression at so-called rest. The abnormally appearing frozen faces of patients receiving a little too much botulinum toxin (see Box 6-3) supports the conclusion that facial expression is actively maintained during waking hours. Further, the resting facial expression is likely to be an emotional action more so than a volitional one. See, for example, the normal resting facial expression made by the patient with volitional facial paresis illustrated in Figure 20-2.

- *Internal:* The actions of people who create art, walk on the beach, or eat ice cream result from internal thoughts, emotions, or motivations.
- *External:* A baby who grabs at glasses or dangling earrings, an adolescent playing a video game, and a sales clerk looking up when the entry bell rings are all reacting to objects or stimuli in the world.

Three cortical regions control actions in rough register with the three reasons for moving:

- Primary motor cortex controls deliberate movements, such as those made in response to another’s request.
- Supplementary motor area controls movements made for internal reasons.
- Premotor cortex controls movements made in response to sensory stimuli.

Since the pathways from language centers that access motor cortex differ from those from visual cortex, which in turn differ from those from somatosensory cortex and so on, lesions in different cortical regions can interrupt actions made for some reasons while leaving acts in service to other goals intact (see Chapter 13). For example, severing the connection between Wernicke’s area and motor cortex will cause an inability to make actions in response to verbal commands. This same lesion spares one’s ability to make the same movement for other reasons, either internal or external. For example, a patient may be unable to pour water from a pitcher in response to a request, but be perfectly able to do so when thirsty. Although rare, this type of disorder, termed *apraxia*, dramatically illustrates the diverse paths leading to action (see Box 16-29).



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CHAPTER 24

CEREBELLUM

The cerebellum is a data-hungry computational powerhouse that specializes in associative learning. Its circuitry and connections are perfectly suited to matching outputs to either static or changing conditions and thereby preventing errors before they happen. The cerebellum makes no assumptions. It is therefore not surprising that the cerebellum does not come “online” until after birth, when the associations between brain activity and the world can first be made from actual evidence.

Judging from the enormous quantity of sensory input it receives, the cerebellum appears to be a *sensory processor*. Yet, cerebellar lesions cause few or no deficits in sensation as such. Instead, most animals and patients with cerebellar disease or injury exhibit dramatically uncoordinated movements, providing compelling evidence for a major cerebellar role in motor coordination. As we shall see, the cerebellum coordinates movements through learning to associate appropriate sensory feedback with intended motor output, an approach whereby the cerebellum utilizes its massive sensory input to regulate and smooth motor function. Since the cerebellum lacks direct connections to α -motoneurons, it exerts its powerful influence on movement through *modulation* of motor control cells in the cerebral cortex and brainstem. Although motor coordination is most obviously impaired by cerebellar dysfunction, the human cerebellum may also modulate nonmotor functions. In this chapter, we examine the role of the cerebellum in movement, in some detail, before briefly considering its potential role in other brain functions.

CEREBELLAR MECHANISMS REMAIN DISPUTED AND CONTROVERSIAL

The basic biology of the cerebellum is beautifully intricate. The clinical importance of the cerebellum is obvious and undisputed. Many have been moved by one or both of these truths to devote their scientific lives to studying and understanding the mechanisms of cerebellar function. Unfortunately, no single version of cerebellar function is without controversy. The core of what I present in this chapter are commonly, although perhaps not universally, held views. When I discuss particularly controversial parts of the story, I indicate them as such.

THE CEREBELLUM COORDINATES THE LEARNING AND PERFORMANCE OF MOVEMENTS INVOLVING MULTIPLE MUSCLES AND JOINTS

Simple movements, involving one or a few muscles acting across only one joint, often proceed without the cerebellum's involvement. In contrast, *the motor circuits of the cerebellum act on movements employing multiple muscles working together across single or multiple joints.* The cerebellum ensures smooth movements through a two-step process:

1. *Motor learning:* After much repetition, at first deliberately executed and then progressively less and less so, movements are learned. Motor memories endure. For example, a person does not forget how to skip, jump rope, or ride a bike.
2. *Motor coordination:* After a multijoint movement is learned, the cerebellum makes its ensuing repetition feel automatic, despite the learned movement's actual complexity. The cerebellum also constantly checks previously learned movements to ensure their smooth completion during challenging as well as ideal conditions.

For learning movements, the cerebellum develops, through practice, a series of associations between motor intention and motor reality—"when cells in one part of motor cortex fire a particular pattern of action potentials, my arm abducts so many degrees, but if these other cells fire, my arm elevates." After much trial and error during infancy and throughout life, *the cerebellum learns to associate actual movements with intended movements.*

Many of our motor memories are of movements that we have repeated millions or billions of times or more. For example, babies learn to stand and walk and then proceed to stand and walk *a lot.* The repetition of trillions of moments of postural sway or billions of walking steps ensures that the cerebellum has learned the motor expectations associated with standing and walking very well. These memories are difficult, if not impossible to forget, even in one who stops walking for months due to an injury. In contrast, someone that learns how to juggle and then practices juggling several hundred times will need more time to "remember" the juggling movements after not juggling for 5 years than after not juggling for 1 day. Yet, eventually, after less time than required initially to learn how to juggle, the motor sequence involved in juggling will come back to even the erstwhile juggler.

Motor memories appear to operate best when done without thinking. Imagine a seasoned pianist sitting down in front of a grand piano on a stage in a concert hall full of people. After the lights dim, the audience applauds and the pianist begins to play. The pianist's playing is automatic, an act linked to the sensory setting and internal feelings by the cerebellum. A pianist who "thinks" too much about performing may freeze or perform poorly and haltingly. Similarly, professional athletes often attribute slumps to "over-thinking" and find that they perform optimally when relaxed and "on autopilot."

The cerebellum's involvement does not stop after a movement is learned. Changing conditions, external and internal, demand that our actual movements be continually measured against our intentions. Therefore, *the cerebellum continually checks for a match between intended and actual movements by determining whether the sensory feedback received matches the feedback that it expects to receive*. With a timed sequence of anticipated feedback information secured in memory, the cerebellum "knows" what sensory feedback to expect and when to expect it for each intended movement. When an already-learned movement goes off track, signaled by errant sensory feedback that deviates from the cerebellum's expectation, the cerebellum triggers an adjustment, so that the received feedback once again matches the anticipated feedback. In this way, the cerebellum coordinates and ensures the smooth performance of semiautomatic movements that we and other mammals are innately destined to learn—standing, walking, running, reaching for food and bringing it to our mouth, looking around—as well as of movements peculiar to our modern lives—driving a car, writing Chinese script, typing on a keyboard, standing on a moving bus.

DIFFERENT CEREBELLAR PARTS REGULATE DIFFERENT TYPES OF MULTIMUSCLED MOVEMENTS

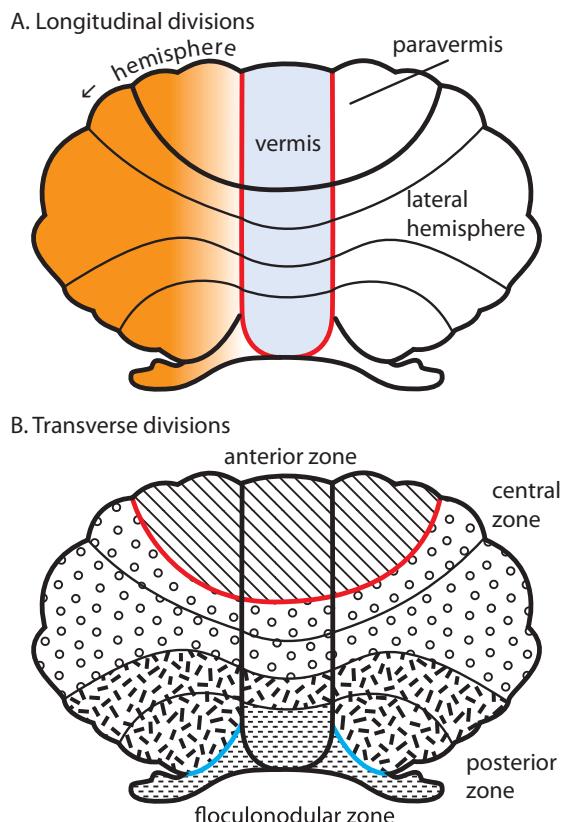
As you recall from Chapter 11, the cerebellar vermis occupies the midline and is flanked by a thin strip termed the *paravermis* and then by the expanse of the lateral hemisphere (Fig. 24-1A). Perpendicular to this broad sagittally oriented organization is a transverse organization of the cerebellum into anterior, central, posterior, and flocculonodular zones (Fig. 24-1B). The flocculonodular zone, consisting of the flocculonodular lobe and the uvula, coordinates eye and head movements with vestibular and visual inputs. This zone, which is often termed the *vestibulocerebellum*, will be discussed in Chapter 26.

There is a broad somatotopy within the cerebellum. The vermis coordinates midline movements: speech, gait, postural control, and stance (see Box 24-1). The paravermis regulates the coordination of movements involving more distal musculature: reaching, grasping, and other appendicular movements. Dysfunction in the paravermis or vermis gives rise to classic ataxic symptoms (see Fig. 11-5).

The lateral portions of the cerebellar hemispheres are largest in animals with highly complex movement repertoires. For example, in a human, the lateral cerebellar hemisphere forms the bulk of the cerebellum and dwarfs the vermis, whereas the reverse is true in the rodent. The entire motor map, including both axial and appendicular muscles, is represented in the lateral hemispheres. The anterior hemispheres are reciprocally interconnected with motor areas of the cerebral cortex, primarily in the frontal cortex. The anterior cerebellar hemispheres are essential to complex motor tasks, tasks initiated by prefrontal cortex that often involve synergistic coordination across the body, actions such as painting, dancing, piano-playing, diving, or singing an aria, as well as in visually guided movements. The posterior portion of the hemispheres connects with nonmotor regions of cerebral cortex and may play important, albeit less widely recognized, roles in language, affect, thought, and executive function.

Figure 24-1. The gross longitudinal (A) and transverse (B) divisions of the cerebellum are diagrammed on a cartoon of a flattened human cerebellum. A: The vermis is an anatomically distinct region separated from the hemispheres by sulci (red lines). In contrast, the lateral edge of the paravermis is indistinct (color gradient). Lateral to the paravermis is the lateral hemisphere. B: The most anterior transverse division of the cerebellum is the anterior zone, which is separated from the rest of the cerebellum by the primary fissure (red line). The most caudal transverse division of the cerebellum is the flocculonodular zone. The hemispheric portion of the flocculonodular zone is separated from the rest of the cerebellum by the posterolateral fissures (blue lines). The vermal portion of the flocculonodular zone includes the nodulus and the uvula (unlabeled). The other two transverse divisions are the central and posterior zones.

Modified from Apps, R., and Hawkes, R. Cerebellar cortical organization: A one-map hypothesis. *Nature Rev Neurosci* 10: 670–81, 2009, with permission of the publisher, Macmillan Publishers Ltd.



Box 24-1

ATAXIA CAN AFFECT EITHER AXIAL OR APPENDICULAR MOVEMENTS.

Paravermis lesions typically produce **appendicular ataxia**, similar to that illustrated in Figure 11-5. In contrast, damage to the vermis, particularly the rostral portion, results in **truncal ataxia**. Truncal ataxia is characterized by a wide stance and unsteady gait much like that of an infant or an intoxicated adult. As with an intoxicated adult, an individual with truncal ataxia is not able to walk heel to toe. Midline cerebellar lesions can also cause ataxic speech, which has an irregular pace and volume, similar to the

speech of an intoxicated person. The similarities between the movements of patients with cerebellar lesions or disease, young infants, and drunken adults is no coincidence. In all three situations, the cerebellum is not working optimally. In young infants, granule cells are still being born, axons have not yet been myelinated, and cerebellar circuits have not been “calibrated.” The mechanisms through which alcohol impairs cerebellar function are not entirely clear and are likely to be varied.

PURKINJE CELLS ORGANIZE THE CEREBELLAR CORTEX INTO PARASAGITTAL STRIPES

Recall that the outer rind of the cerebellum is a cortex and that the *Purkinje cell* is a cerebellar cortical neuron with an apical dendrite that extends toward the pial surface (see Box 13-1). The Purkinje cell has a remarkable anatomical appearance. First, Purkinje cells form a layer within the cerebellar cortex that is one cell wide (Fig. 24-2A). In other words, Purkinje somata are lined up like box cars with absolutely no stacking. The apical dendrite branches exuberantly, and the entire dendritic arbor is covered with spines. Yet, the Purkinje cell dendrites are tightly organized within a plane that is perpendicular to the folia; for most of the cerebellum, perpendicular to the folia means in a sagittal section (Fig. 24-2B). Thus, the Purkinje cell dendritic tree is narrow, about the width of the soma, in the plane of the folia, but measures hundreds of microns across in the perpendicular plane. In short, the Purkinje cell dendritic tree is oriented like a Mohawk hairdo.

Recently, the idea has been put forth that the orientation of Purkinje cell dendrites dictates the organization of the cerebellar cortex (see Apps and Hawkes, 2009, in “Additional readings”). According to this idea, which has not gained universal acceptance yet, Purkinje cells within parasagittal stripes, oriented from rostral to caudal, form functional groupings or microdomains. The stripes occupied by the

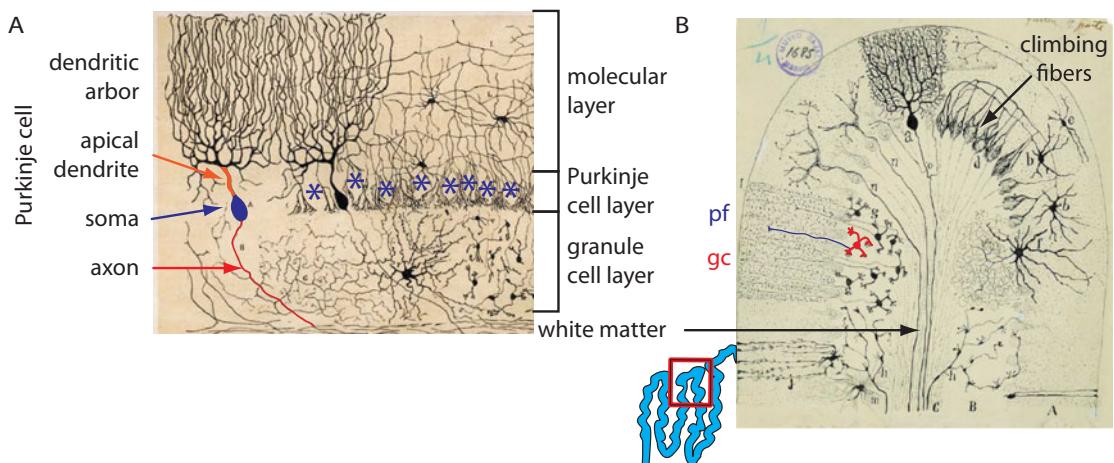


Figure 24-2. The cerebellar cortex is intricately organized, as originally described and drawn by Ramón y Cajal. These modified drawings from Cajal show the basic laminated structure of the cerebellar cortex and illustrate the cell and afferent fiber types discussed in the text. **A:** Cerebellar cortex has a cell-poor molecular layer, a Purkinje cell layer, and a granule cell layer. The Purkinje cell layer contains the somata of Purkinje cells. One such soma is colored in blue and labeled. An additional Purkinje cell soma is drawn in black. The climbing fibers innervate Purkinje cells so densely that the somata are outlined by the afferent fibers. The blue asterisks show the location of Purkinje cells present at the center of such concentrations of climbing fibers. The Purkinje cell sends an axon into the white matter below, and this axon eventually terminates in the appropriate deep cerebellar nucleus. The apical dendrite of the Purkinje cell branches extensively to form an elaborate dendritic arbor. **B:** A drawing of a transverse section through a folium shows a Purkinje cell (*top*), climbing fibers, the underlying white matter, and a number of granule cells. One granule cell (*gc*) is colored red, and its axon, which gives rise to a parallel fiber (*pf*), is colored in blue. The granule cell axon travels into the molecular cell layer, bifurcates, and then extends for up to millimeters in the medial-lateral direction, in and out of the plane of the paper.

Drawings are adapted from Sotelo, C. Viewing the brain through the master hand of Ramón y Cajal. *Nature Rev Neurosci* 4: 71–7, 2003, with permission of the publisher, Macmillan Publishers Ltd.

functional units only extend a short distance in the caudal to rostral direction. Consequently, there are thousands of microdomains in the cerebellum, and each functional grouping contains a few hundred Purkinje cells. We consider the functional meaning of these cerebellar microdomains after examining the organization of the output from the cerebellar cortex.

THE DEEP CEREBELLAR NUCLEI PROVIDE THE SOLE SOURCE OF CEREBELLAR OUTPUT TO THE REST OF THE BRAIN

Deep to the cerebellar cortex is white matter (Fig. 11-6), and deep within the white matter are bilateral sets of **deep cerebellar nuclei** (Fig. 24-3). Neurons in the deep cerebellar nuclei carry the output of the cerebellum to the brainstem and thalamus. Note that all cerebellar neurons reside in either the *cerebellar cortex* or the deep cerebellar nuclei. The deep cerebellar nuclei receive input from the cerebellar cortex in a topographical fashion:

- Cerebellar cortex within the vermis projects to a pair of deep cerebellar nuclei, the **fastigial** nuclei, situated just off midline.
- Each paravermis projects to an **interposed** nucleus, located lateral to the fastigial nucleus. On each side, there are two interposed nuclei—*posterior* and *anterior*—which are often called the **globose** and **emboliform** nuclei in older texts.

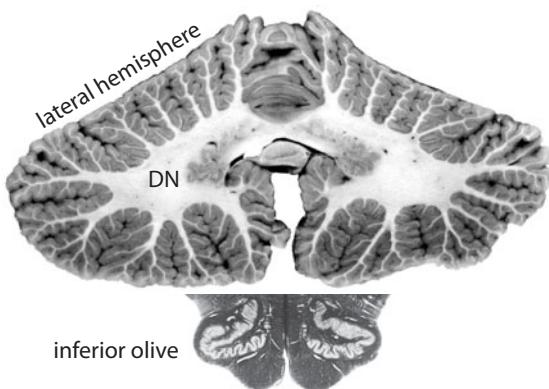


Figure 24-3. An unstained section through the cerebellum (top) and a myelin-stained section through the medulla (bottom) illustrate the relationship between the outlines of the lateral cerebellar hemisphere, dentate nucleus (gray matter labeled DN), and inferior olive. The resemblance between the outside contours of these three structures stem from their anatomical relationships. Cells in the main inferior olivary nucleus project topographically to Purkinje cells in the lateral hemisphere, and Purkinje cells in the lateral hemisphere in turn project topographically to the dentate nucleus.

Top photograph reprinted with permission from deArmond S., et al. *Structure of the human brain: A photographic atlas*. New York: Oxford University Press, 1989. Bottom photograph reprinted with permission from Bruni, J.E., and Montemurro, D. *Human neuroanatomy: A text, brain atlas, and laboratory dissection guide*. New York: Oxford University Press, 2009.

- The lateral hemispheres project to the large **dentate** nuclei whose elaborate shape resembles the contour of the hemispheres themselves (Fig. 24-3).

In addition to the gross somatotopy of cerebellar cortex to deep cerebellar nuclei projections—vermis to fastigial, paravermis to interposed and lateral hemispheres to dentate—there is an extremely fine topography. Essentially, neighboring Purkinje cells project to neighboring deep cerebellar nuclear neurons. This means that the Purkinje cells in one microdomain project to a patch of neighboring deep cerebellar nuclear neurons. Since neurons in each deep cerebellar nucleus send axons out of the cerebellum to reach specific brainstem and diencephalic targets, Purkinje cells in one microdomain ultimately influence one motor control center. One final important aspect of the microdomains is that neighboring Purkinje cells *receive* input from neighboring cells in the inferior olives. Because of the fine topography between inferior olives, Purkinje cells, and the deep cerebellar nuclei, the three areas actually resemble each other in appearance. This resemblance is most clearly seen by comparing the outlines of the lateral cerebellar hemisphere, the dentate nucleus, and the principal portion of the inferior olive (Fig. 24-3).

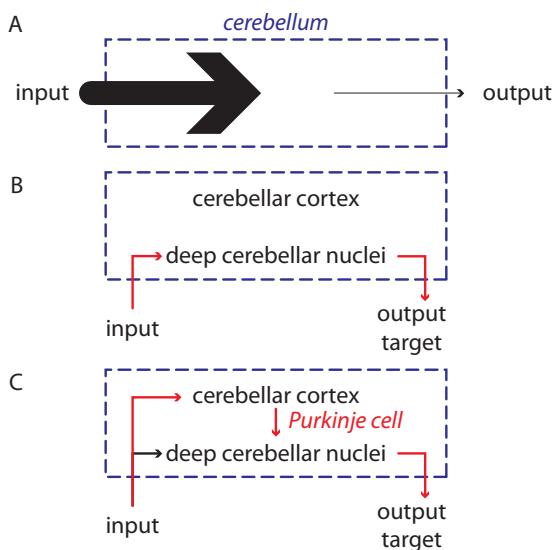
In sum, the specific function of cerebellar cortical processing is shared by Purkinje cells in a microdomain. The idea is that Purkinje cells within a single functional unit influence the contribution of a particular motor control center to a particular type of movement via a projection to a restricted region in the deep cerebellar nuclei. For example, 30-40 microdomains may be responsible for modulating rubrospinal control of the foot withdrawal reflex, with each different microdomain primarily concerned with withdrawals evoked from a restricted area of skin and employing a different primary muscle (see Chapter 22). Similarly other groups of microdomains modulate corticospinal control of wrist movements or vestibulospinal control of postural sway and so forth.

INFORMATION PASSES THROUGH TWO LOOPS WITHIN THE CEREBELLUM

An enormous amount of information comes into the cerebellum and targets both the cerebellar cortex and the deep cerebellar nuclei, the only two cerebellar regions containing neurons. The number of axons coming into the cerebellum outnumbers the number of axons that leave the cerebellum by a factor of 40 (Fig. 24-4A). This extreme degree of convergence reflects the combined processing power of the cerebellar cortex and the deep cerebellar nuclei.

Since neurons of the deep cerebellar nuclei carry the entire output of the cerebellum to the brainstem and forebrain, the simplest cerebellar loop (Fig. 24-4B) consists of only one cerebellar synapse, the synapse between incoming fibers and a deep cerebellar nuclear neuron. A second pathway loops through the cerebellar cortex (Fig. 24-4C), which processes incoming information, transforming it into a *single* coherent message carried by the Purkinje cell, the only cell type in the cerebellar cortex that projects out of the cortex. The Purkinje cell targets neurons in the deep cerebellar

Figure 24-4. The basic inputs and outputs of the cerebellum are diagrammed. A: There are 40-times more afferent axons into the cerebellum (thick black arrow) than there are efferent axons from the cerebellum (thin black arrow). B: The simplest circuit through the cerebellum involves input to deep cerebellar nuclear neurons, which send axons out of the cerebellum to target structures. C: More processing power is contained in the circuit through the cerebellar cortex than the one diagrammed in B. Afferents to the cerebellum project to the cerebellar cortex. After processing in the cerebellar cortex, involving multiple neurons, Purkinje cells within the cerebellar cortex send an axon to the deep cerebellar nuclei. Deep cerebellar nuclear neurons send an axon out of the cerebellum to a target structure in the brainstem or thalamus. Note that the Purkinje cell is the only cell that projects out of the cerebellar cortex.



nuclei, which then carry the final cerebellar message to the brainstem and forebrain. This second loop includes several synapses within the cerebellar cortex and provides the cerebellum with an enormous amount of additional processing power.

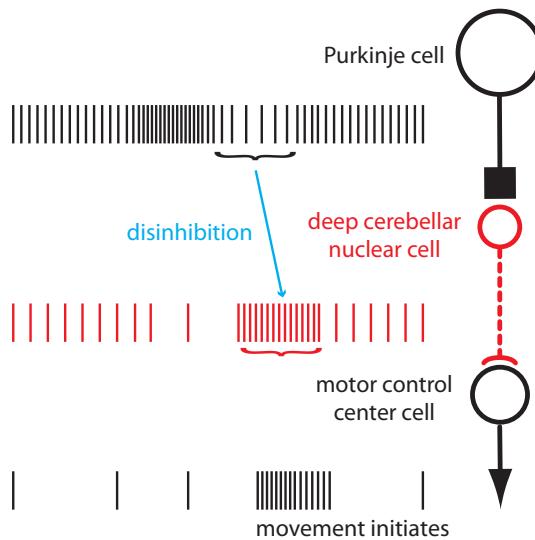
Although neurons in both the cerebellar cortex and the deep cerebellar nuclei transform incoming information, the cerebellar cortex surpasses the deep cerebellar nuclei in processing power. The cerebellar cortex is particularly important in learning new movement combinations. All together, the speed and informational throughput of cerebellar processing far surpasses and is in fact in a different galaxy than that of even the most sophisticated computer chips.

As one consequence of the basic cerebellar circuits, *injury to the deep cerebellar nuclei or to the output of the deep cerebellar nuclei, principally carried in the superior cerebellar peduncle, will mimic an injury to the cerebellum itself*. A lesion of the decussation of the *brachium conjunctivum*, or superior cerebellar peduncle, will look like a lesion of almost the entire cerebellum. Incomplete lesions of the cerebellar output give rise to symptoms like those caused by lesioning upstream regions. So, for instance, a lesion of the fastigial nucleus will look like a lesion of the vermis. In contrast, injuries to the cerebellar cortex cause less severe and less permanent symptoms than do those to the deep cerebellar nuclei.

PURKINJE CELLS INHIBIT DEEP CEREBELLAR NUCLEAR NEURONS THAT POWERFULLY FACILITATE MOVEMENT

Purkinje cells contain γ -aminobutyric acid (GABA) and are therefore inhibitory. Purkinje cells are also spontaneously active (Fig. 24-5). As one would expect, the deep cerebellar nuclear neurons are also spontaneously active. Purkinje cells fire at typical rates of 50 to more than 200 Hz, whereas deep cerebellar

Figure 24-5. Purkinje cells are GABAergic cells that inhibit deep cerebellar nuclear neurons. The firing patterns of three connected cells are diagrammed. Each vertical line represents an action potential. At rest, Purkinje cells fire more rapidly than do either deep cerebellar nuclear neurons or cells in motor control centers. When the discharge rate of the Purkinje cell increases, the deep cerebellar nuclear neuron fires less rapidly, and when the discharge rate of the Purkinje cell decreases, the deep cerebellar nuclear neuron is disinhibited. Disinhibition results in an increase in the firing rate of the postsynaptic cell, and in this case, in a burst of activity in the motor control center cell. This burst of activity can initiate a movement.



nuclear neurons fire at slightly more modest rates, commonly about 20–50 Hz. When Purkinje cells increase their firing rate, deep cerebellar nuclear neurons are inhibited, maybe even pausing. In contrast, when there is a relative lull in Purkinje cell firing, deep cerebellar nuclear neurons are *relieved from inhibition*, a process termed **disinhibition** (Fig. 24-5). Disinhibition involves a decrease in incoming inhibition. The firing rate of the postsynaptic cell—in this case, a deep cerebellar nuclear neuron—then increases. Thus, when Purkinje cell firing slows, the discharge of targeted deep cerebellar nuclear neurons increases.

Deep cerebellar nuclear neurons powerfully excite their target neurons in the thalamus and brainstem, which in turn causes excitation of motor control centers. Thus, *cerebellar output strongly facilitates cerebellum-coordinated movement to such an extent that deep cerebellar nuclear neurons play an important role in the initiation and cessation of movements* (Fig. 24-5). Activity in deep cerebellar nuclear neurons occurs before movements start and cerebellar dysfunction leads to slower movements. When deep cerebellar nuclear neurons stop firing, movement stops too. In sum, the cerebellum exerts a strong excitatory effect upon motor control centers and ultimately upon *movement*. Lesions or injuries to the cerebellum, particularly to the deep cerebellar nuclei, often result in a loss of tone, termed **hypotonia** (see Box 24-2).

THE CEREBELLUM USES SENSORY AND CORTICAL INPUTS TO ORCHESTRATE THE CONTRIBUTIONS OF MULTIPLE MUSCLES TO COORDINATED MOVEMENTS

The cerebellum anticipates the muscle coordination necessary for smooth movements, ensuring that the movements that we make are those that we intend to make. For example, when we reach for a cup handle, anything short of reaching the handle is a failure. Yet, it would not work to spend our lives

MUSCLE TONE IS IMPAIRED BY DEEP CEREBELLAR NUCLEAR LESIONS.

Since neurons in the deep cerebellar nuclei are excitatory and lead to activation of neurons in motor control centers, lesions of the *deep cerebellar nuclei* decrease muscle tone and slow movements permanently. In contrast, activity in the cerebellar cortex indirectly decreases activity in motor control centers. Lesions in *cerebellar cortex* have little or no effect on muscle tone.

practicing all the possible situations that may call for this movement: reaching for differently sized cup handles located above or below you, near or far from you, a cup that is sitting upright or hanging on a hook. Instead, the cerebellum learns a number of different movement basics—arm extension, abduction, wrist pronation, grasp, and so on. Then, to perform a multimuscled, multijointed movement such as reaching for a cup, the cerebellum combines these basic movements together by sending accurately timed signals to motor control centers to generate the correct forces in specific muscles, each at the right time. In this way, the cerebellum is akin to a conductor: the conductor plays no musical instrument but coordinates the musicians, so that one section starts up just as another section pauses. Similarly, the cerebellum does not contract muscles but tells motor control centers when to activate which muscles in what order to achieve a well-orchestrated movement.

To accomplish its tasks, the cerebellum uses two primary types of information (Fig. 24-6):

- **Reafference** is sensory information, coming back into the central nervous system (CNS) from the periphery, about the movement actually occurring.
- **Efference copy**, also called **corollary discharge**, is a neural copy of the intended or desired action.

We term sensory information arising from joints, muscles and skin as “reafference” because it is sensory (affection) feedback back (re-) from a motor program that we are executing. Think of a pilot’s pressing a button to lower the wing flaps and then receiving feedback from sensors signaling that the wing flaps are indeed

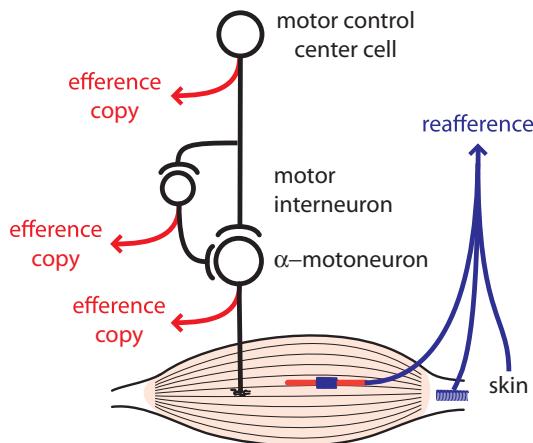


Figure 24-6. The sources of efference copy and reafference are shown on a diagram of the basic motor hierarchy. A motor control cell in the cerebral cortex contacts motoneurons and motor interneurons and sends efference copy information to the cerebellum via the pontine nuclei. Additional efference copy input derived from the discharge of motoneurons and motor interneurons arises from the ventral horn and is carried by spinal border cells into the cerebellum. Reafference information comes primarily from cutaneous mechanoreceptors and also from muscle afferents. Reafference input to the cerebellum is carried by spinal and medullary cells that receive primary afferent input from the dorsal columns. Note that in all cases, there is an intermediary cell, or a *pre-cerebellar* cell, between the source of the input (motor control center, motor interneuron, motoneuron, primary afferent) and the cerebellum.

in the down position; this feedback from sensors is akin to reaference. *In ideal circumstances, we would receive no surprises from reaference. Information coming back from the periphery to the cerebellum would match exactly the expected information, so that the movement would “feel right.”* However, in myriad situations, such as an unexpectedly soft spot in the ground, intended movements must be adjusted to changing conditions. In such situations, one often knows the exact moment when a movement veers off course: the returning input “feels wrong” of a sudden.

Clearly, in order to render reaference meaningful, an expected outcome is required. *Information about the expected movement is carried by an efference copy signal that serves as the gold standard to which actual movement is compared.* If reaference matches efference copy, all is well. However, when there is a mismatch, the cerebellum dictates appropriate adjustments. As the cerebellum modulates movement in a **feed-forward** fashion, it corrects *future* iterations of an errant movement. Thus, when stepping off the sandy beach and onto the sidewalk, the first step is too forceful, more appropriate for the sand than for concrete. The cerebellum quickly adjusts the gait, so that ensuing steps are appropriate.

MOSSY FIBERS CARRY REAFFERENCE AND EFFERENCE COPY INPUTS TO THE CEREBELLAR CORTEX AND DEEP NUCLEI

Virtually all of the input to the cerebellum is carried by a heterogeneous group of afferents called *mossy fibers*, which travel primarily in the middle and inferior cerebellar peduncles. In fact, all afferent inputs to the cerebellum, *except* for inputs from the inferior olives, are mossy fibers. The axons of inferior olive neurons, which travel through the restiform body, are called *climbing fibers*. Mossy fiber input is *massive* in number and effect, providing the major excitatory energy that drives the cerebellum. Mossy fibers enter the cerebellum, travel through the white matter, and terminate in two places (Fig. 24-4C):

Box 24-3

THERE ARE MORE GRANULE CELLS THAN NEURONS OF ANY OTHER TYPE.

The number of **granule cells** is truly staggering, approaching half of all the neurons in the brain (about 10^{11}). Generating all of these neurons from the rhombic lip happens primarily after birth and requires years for completion.

- *Deep cerebellar nuclei:* mossy fibers directly excite the neurons that project out of the cerebellum.
- *Cerebellar cortex:* mossy fibers excite **granule cells** (see Box 24-3) that in turn indirectly excite Purkinje cells.

Mossy fibers arise from a number of sources but primarily from:

- The periphery via spino- and cuneocerebellar tracts
- Motoneurons, motor interneurons, and central pattern generators via spino- and cuneocerebellar tracts
- Vestibular information, arriving via the vestibular nerve and nuclei

- Cortex, including motor, premotor, somatosensory, and visual areas, via a synapse in the pontine nuclei

Mossy fibers carry reafference input and efference copy. Thus, *mossy fiber discharge increases by virtue of sensory input, of any modality, and from efference copy during self-generated movements.*

Several mossy fibers converge onto each granule cell, which in turn sends out an axon that travels toward the pial surface, through the Purkinje cell layer, and bifurcates within the molecular layer into two long branches, termed **parallel fibers**, that travel along the long axis of the folia (Fig. 24-7A). Since parallel fibers travel perpendicularly to the orientation of the Purkinje cell dendrites, each parallel fiber contacts the dendrites of a multitude of Purkinje cells spread over many millimeters (Fig. 24-7B). This means that *information from a mossy fiber that contacts a granule cell within one region of the cerebellum is distributed to Purkinje cells in near and distant regions.* So, for example, information that comes into the paravermis may reach the vermis via the far-reaching parallel fibers. This allows a Purkinje cell in the vermis that controls trunk musculature to “know” at least a little bit about what, for example, the hand is doing.

The Purkinje cell’s processing of mossy-parallel fiber input represents the computational bottleneck of the cerebellar cortex: *each Purkinje cell receives input from up to 200,000 parallel fibers and thus indirectly from a million or more mossy fibers* (Fig. 24-7B). The effect of discharge in one parallel fiber upon a Purkinje cell is small, either resulting in an excitatory postsynaptic potential (EPSP) or a single action potential, which is termed a **simple spike**. Yet, *the Purkinje cell receives such a multitude of synapses from parallel fibers that mossy fiber input constitutes the major excitatory drive on Purkinje cells.*

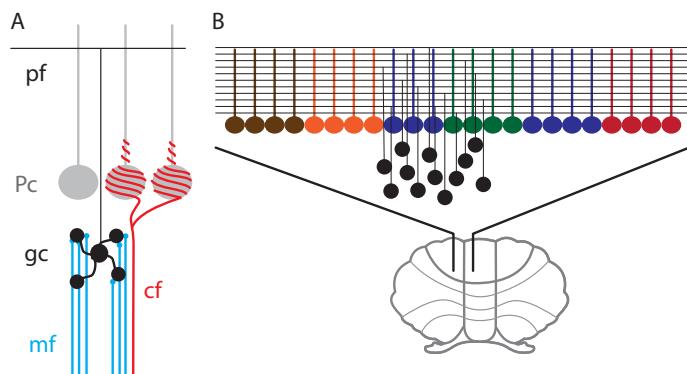


Figure 24-7. Cerebellar circuitry is diagrammed in the coronal plane. In this plane, the dendritic arbor of the Purkinje cells (**Pc**) is narrow and is represented here as simply a line. **A:** Purkinje cells receive indirect input from mossy fibers (**mf**). Many mossy fibers end on each granule cell (**gc**). Each granule cell sends an axon up into the molecular layer. The granule cell axon bifurcates into a parallel fiber (**pf**), which extends for long distances in the longitudinal plane of the folia. Along the way, a parallel fiber can contact thousands of Purkinje cells, and each Purkinje cell receives hundreds of thousands of synapses from parallel fibers. The second source of afferent input to the Purkinje cell is the climbing fiber (**cf**), which arises from the inferior olive. A climbing fiber innervates a few to several Purkinje cells, but each Purkinje cell receives input from only one climbing fiber. **B:** Recall that Purkinje cells form functional units or microdomains that are oriented as short sagittal stripes in the rostral to caudal direction. Here, Purkinje cells belonging to distinct microdomains are denoted by different colors. The parallel fibers arising from granule cells extend across many microdomains and can even cross the midline or between different longitudinal divisions of the cerebellum (see Fig. 24-1).

THE CEREBELLUM IS CRITICAL TO THE PROPER TERMINATION OF MOVEMENTS

Just as a piece of symphonic music depends upon the proper timing of orchestral members, coordinated movement depends upon correctly timing the activations of several different muscles, all contributing to a single movement. Furthermore, just as coordinated timing is more important to a symphony than to an individual musician playing a solo, cerebellar coordination is more important to movements that involve multiple muscles than to those involving one muscle or a small group of muscle synergists. Thus, the cerebellum is far more important to extending one's arm to ring a doorbell than to extending one's arm to its full extent, as when raising one's hand in class. The former requires that the antagonist contracts at precisely the correct moment to stop the momentum provided by the agonist contraction, whereas the latter only requires contraction of the primary agonist muscle group, with the stop provided by arm mechanics. From these two examples, the reader should understand that accurately ending a movement at a target is difficult. In other words, the end of a targeted reach is more difficult to produce than the beginning.

Let us once again consider the example of reaching for a cup handle. To extend the arm, the triceps needs to be activated, but once the arm nears the cup, the triceps activation needs to be terminated and the biceps activated as a brake. Mossy fiber input signals the intended movement and contributes to excitation of motor cortex cells that initiate triceps contraction. As the hand nears the cup handle, Purkinje cells burst and deep cerebellar nuclear neurons pause, terminating the triceps contraction. Just as the arm extension ends, arm flexion is initiated, allowing for the smooth and accurate reaching of the cup handle. If arm flexion occurred too early or too late, the target would be undershot or overshot, respectively. Making movements that are too short or too long is termed **dysmetria**. Since, as described above, the trickiest part of all of this is anticipating movement termination, cerebellar lesions and disease tend to result in **hypermetric** movements—movements that reach beyond their targeted goal. The critical contribution of the cerebellum to starting and stopping movements is particularly evident in the performance of rapidly alternating movements (see Box 24-4).

Box 24-4

RAPIDLY ALTERNATING MOVEMENTS ARE COORDINATED BY THE CEREBELLUM.

The cerebellum is particularly critical to correctly terminating movements. As a result, patients with cerebellar dysfunction are especially poor at starting and stopping movements rapidly. One way to test for this ability is to ask a person to move their palm up and down rapidly. Such a quickly alternating movement requires tight coordination between supinating and pronating forearm muscles that move the palm up and down. The inability to make rapidly alternating movements is termed **dysdiadochokinesia** and is diagnostic of a cerebellar problem.

The cerebellum provides the coordination required to accurately target movements. Moreover, cerebellar coordination operates in anticipation, in a *feed-forward* manner. Thus, in the absence of the cerebellum, mistakes are made and only *after* they are made are they corrected. This type of error occurs in **ataxia**. Ataxic movements involve an abnormal sequence of muscle contractions and relaxations, with the error being greatest as the target is neared. Ataxic movements result from the replacement of anticipatory modulation with feedback corrections. Figure 24-8 shows the movement trajectories of control subjects and subjects with an inherited form of ataxia on two different tasks. In one task, subjects were asked to move their hand through a target into a soft barrier that stopped their arm's forward movement, whereas in the other task, subjects were asked to move their hand to a square and stop there. Patients' arm trajectories on the former task, in which a barrier ended the movement, were indistinguishable from those of control subjects. In contrast, patients overshot the target in the latter task and subsequently made

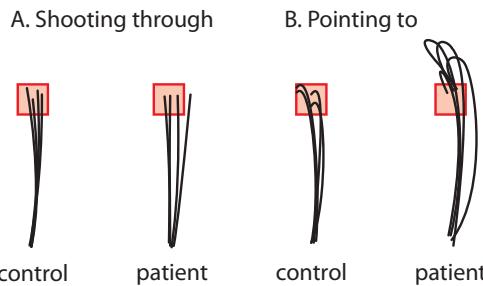


Figure 24-8. Control subjects and patients with inherited spinocerebellar ataxia were asked to move a joystick on a trajectory that passed through but did not stop in the red square (A) or to move the joystick into the square and stop there (B). The lines indicate the trajectories on four attempts by each subject at this task. Control and patient trajectories were very similar on the “shoot through” task. However, on the pointing task, control subjects’ trajectories all ended within the target square, whereas the patients’ trajectories all overshot (= hypermetria) and then had to come back to the target.

Adapted from Tseng, Y., Diedrichsen, J., Krakauer, J.W., Shadmehr, R., and Bastian, A.J. Sensory prediction errors drive cerebellum-dependent adaptation of reaching. *J Neurophysiol* 98: 54–62, 2007, with permission of the publisher, American Physiological Society.

a corrective return movement. As illustrated by this example, patients with cerebellar dysfunction typically make hypermetric movements that overshoot the target. Such patients find that they need to make movements quite deliberately, “thinking” through each piece of the movement. This leads to slower movements and to a **decomposition of movements** into their component parts (see Box 24-5).

Box 24-5

CEREBELLAR CORTEX LESIONS LEAD TO DECOMPOSITION OF AGONIST–ANTAGONIST MOVEMENTS.

Lesions of the cerebellar cortex cause ataxia, in which agonist–antagonist muscle pairs no longer activate in a coordinated fashion. Feedback corrections occur after mistakes have been made, resulting in an overshoot or hypermetria. Since the component parts of a movement are no longer timed correctly in advance, the component parts happen sequentially, which appears as a **decomposition of movement**. In the absence of continued degeneration, ataxic symptoms generally remit over time, presumably because the cerebellum learns anew.

CLIMBING FIBERS ARE KEY TO CEREBELLAR LEARNING

As the reader can imagine, correctly anticipating the effects of muscle contractions is the key to proper cerebellar function. Remember that most cerebellar neurons are born, receive afferents, and receive myelination on their axons postnatally, at a time when a baby can learn to associate motor commands with their consequent physical effects. After the cerebellum has developed and an infant has spent sufficient time playing, babbling, and gesticulating, seemingly without purpose, cerebellar neurons have learned enough from past motor experiences to “know” what reaference to expect from a given movement. By anticipating the correct reaference, the cerebellum can prevent errors before they occur. So, movements, at least simple ones, are “spot-on” even when performed for the first time. A child who learns how to take her sippy cup from a parent can also pick up the cup from the floor. Even when physical conditions change—imagine the sippy cup being either nearly empty or completely full—the cerebellum quickly learns how those changes will alter the anticipated feedback and thereby adjusts the movement after minimal disruption.

Climbing fibers arise only from the contralateral inferior olive, enter the cerebellum through the restiform body, and excite Purkinje cell dendrites directly. Each climbing fiber wraps itself around the soma and dendrites of 5–20 Purkinje cells that are contained within a single micro-domain (Fig. 24-7A). Climbing fibers do not fire rapidly, discharging irregularly at an average rate of about once per second. The climbing fiber to Purkinje cell is a very strong synapse in the CNS; an action potential in a climbing fiber elicits a depolarization plateau on which about five action

potentials ride in the postsynaptic Purkinje cell. This response is termed a **complex spike**. Yet, inactivation of climbing fibers results in an *increase*, rather than a decrease, in Purkinje cell firing, suggesting that *the net effect of climbing fiber input is actually suppression of Purkinje cell firing*. The apparent climbing fiber inhibition of Purkinje cells results from factors including:

- *Activation of inhibitory interneurons in the cerebellar cortex.* Climbing fibers excite interneurons that in turn inhibit Purkinje cells. Although interesting, the rich and intricate contributions of inhibitory interneurons to cerebellar function are beyond the scope of this text.
- *Complex spike firing is followed by a large after-hyperpolarization.* After a climbing fiber elicits a complex spike in a Purkinje cell, the Purkinje cell hyperpolarizes, imposing a pause in subsequent firing.
- *A decrease in the efficacy of simultaneously firing parallel fiber synapses, both during climbing fiber firing and afterward.* This enduring suppression of parallel fiber synapses by climbing fiber input is a form of long-term synaptic depression.

Climbing fibers provide a teaching signal that tells the Purkinje cell what set of parallel fiber inputs to anticipate and when to anticipate these inputs for any given intended movement. (Note that the function of the climbing fibers is the subject of perhaps the oldest controversy in the cerebellar field and that this controversy rages to this day without a unanimously accepted solution.) Repeated practice of a movement trains the cerebellum to associate a set of reafference input with a particular efference copy message. Imagine stepping onto a boat for the first time. The feed-forward adjustments that allowed for postural stability and a balanced gait on land will fall short at sea. You will have to use your cerebellum to modify your postural control and gait programs over the course of several days. In other words, you need to “get sea legs.” Yet, even as you learn the sea-legs program, you do not forget how to walk on land. This illustrates the cerebellum’s ability to learn and retain multiple, distinct motor programs that operate on the same body parts. These motor programs do not interfere with each other, nor do they degrade over time. Thus, a sailor who returns to land after months at sea can quickly return to normal terrestrial walking and standing. Similarly, after establishing cerebellum programs for walking, marching, running, and cycling, one can seamlessly and perfectly switch between these motor activities without bleed-through of one activity into another.

DIFFERENT REGIONS OF THE CEREBELLUM AFFECT DIFFERENT TYPES OF MOVEMENTS THROUGH PARTICIPATION IN DISTINCT CIRCUITS

The entire cerebellum processes mossy and climbing fiber inputs in the same basic way. However, the signals contained in inputs destined for different parts of the cerebellum differ. Similarly, the outputs from the vermis,

paravermis, and lateral hemispheres differ. In the next few sections, the major inputs to and outputs from the vermis, paravermis, and lateral hemispheres are described.

INFORMATION ABOUT INTENDED AND ACTUAL MOVEMENTS ARISE FROM SPINO- AND CUNEOCEREBELLAR TRACTS-

The cerebellum receives direct reaference and efference copy about the arms, trunk, and legs from four different tracts ascending from the spinal cord and caudal medulla (Table 24-1). Two tracts carry direct reaference—one from the legs and trunk and one from the arms—and two carry direct efference copy—again one from the legs and trunk and one from the arms. Indirect reaference comes from the inferior olivary nucleus and indirect efference copy input comes from the **lateral reticular nucleus** located in the caudal medulla.

Reaference input arises from secondary sensory neurons, meaning neurons that receive primary afferent input. These secondary sensory neurons are located in the spinal cord in the case of the legs and in the caudal medulla in the case of the arms. Leg and trunk proprioceptive information comes from neurons in **Clarke's nucleus**, located in the thoracic spinal cord (see Fig. 9-9), via the **dorsal spinocerebellar tract**. Arm proprioceptive input arises from the **external (or accessory) cuneate nucleus** (just lateral to nucleus cuneatus) and travels in the **cuneocerebellar tract**. Both the dorsal spinocerebellar and cuneocerebellar tracts course through the restiform body and enter the cerebellum through the inferior cerebellar peduncle.

Spinal border cells located in the ventral horn receive copies of motoneuron and motor interneuron discharge and give rise to two tracts that carry efference copy into

TABLE 24-1. THE FOUR MAJOR PRECEREBELLAR TRACTS ARISING FROM THE SPINAL CORD AND CAUDAL MEDULLA ARE LISTED

	DORSAL SPINOCEREBELLAR TRACT	VENTRAL SPINOCEREBELLAR TRACT	CUNEOCEREBELLAR TRACT	ROSTRAL SPINOCEREBELLAR TRACT
Type of information	Reaference	Efference Copy	Reaference	Efference Copy
Body parts	Legs and trunk	Legs and trunk	Arms	Arms
Arises from	Clarke's nucleus	Ventral horn	External cuneate nucleus	Ventral horn
Enters through	Restiform body/ Inferior cerebellar peduncle	Superior cerebellar peduncle	Restiform body/ Inferior cerebellar peduncle	Restiform body/ Inferior cerebellar peduncle

Two tracts carry reaference information and two tracts carry efference copy input. One tract carrying input of each type concerns the legs and trunk and one tract of each type concerns the arms. The cells of origin for each tract as well as the cerebellar peduncle through which the tract enters the cerebellum are also listed. The restiform body is a tract that forms the bulk, but not all, of the inferior cerebellar peduncle. The other tract within the inferior cerebellar peduncle is the juxtarestiform body, which contains the output from the fastigial nucleus bound for reticular and vestibular nuclei.

the cerebellum. Spinal border cells in the lumbosacral and cervical cords carrying efference copy information give rise to the **ventral** and **rostral spinocerebellar tracts**, respectively. Like the tracts carrying reaference information, the rostral spinocerebellar tract enters the cerebellum through the inferior cerebellar peduncle. The ventral spinocerebellar tract is unusual in two ways:

- The ventral spinocerebellar tract enters the cerebellum through the **superior** cerebellar peduncle and is the only afferent tract to do so.
- The ventral spinocerebellar tract crosses within the spinal cord, whereas the other spinocerebellar and cuneocerebellar tracts travel ipsilaterally. The ventral spinocerebellar tract crosses again upon entering the superior cerebellar peduncle, thus terminating ipsilateral to its site of origin.

As the vermis is most involved in controlling axial musculature including the head, it is not surprising that the vermis also receives vestibular, auditory, visual, and proprioceptive input from eye, head, neck, and shoulder muscles.

INFORMATION FROM THE CEREBRAL CORTEX REACHES THE CEREBELLUM BY WAY OF THE PONTINE NUCLEI

The cerebellum receives a *massive* amount of input from most parts of the cerebral cortex. Cerebral cortical neurons do not project directly to the cerebellum but rather project to pontine nuclear neurons. Pontine nuclear neurons in turn send an axon across the midline, through the middle cerebellar peduncle, and into the cerebellum (see Fig. 11-3). The basis pontis and middle cerebellar peduncle are entirely utilized by the pathway from cerebral cortex to cerebellum. The enormity of these two structures embodies the scale of the connection from cerebral cortex to cerebellum.

As the reader understands, the cerebral cortex and cerebellum are not so far apart that one neuron could not traverse the entirety of the distance. Yet, cortical neurons only access the cerebellum through the pontine nuclei. The obvious implication is that pontine neurons contribute to the translation or compilation of cerebral cortical information for the cerebellum. Unfortunately, we know and understand little about pontine nuclear function at present.

Motor-related input from the cerebral cortex destined for the cerebellum arises from the somatomotor and prefrontal cortices. There are particularly strong projections from motor, supplementary motor area, somatosensory, and parietal association cortices. Much of the input from frontal cortex carries information about movements that are being made or are being mentally rehearsed. Thus, at least some of the input from frontal cortex appears to be a cortical complement to the spinal efference copy carried by the ventral and rostral spinocerebellar tracts.

THE CEREBELLUM IS CRITICAL TO MODULATING GAIT.

As you recall from Chapter 22, central pattern generators in the lumbar spinal cord support the basic stepping cycle or gait. Yet, even in our modern world, stepping needs to be adjusted to the task at hand and to the environment. Slowing down to walk with a child, speeding up to get to class on time, turning, and walking up a rocky incline all require modifications of gait. The cerebellum coordinates these modifications, and recent evidence shows that the cerebellum contributes to the coordination of the left and right legs' step cycles. The belt on a treadmill can be split so that the left and right halves of the treadmill are controlled independently. A person walking on a split-belt treadmill matches each leg's gait to its half belt so that, for example, the right leg may be going at a faster speed than the left leg. Remarkably, people are even able to walk in different directions with their two legs—stepping forward with one leg and backward with the other. A healthy person's ability to perform this "cerebellar task" depends on performing it without thinking about it directly, in an automatic-like fashion. Individuals with cerebellar disease or lesions cannot walk on a split-belt treadmill, evidence that this type of gait modulation depends on a working cerebellum.

THE OUTPUT OF THE VERMIS TARGETS DESCENDING POSTURAL CONTROL AND ORIENTING TRACTS

The output of the vermis reaches motor centers primarily concerned with postural control and orienting movements. Purkinje cells in the vermis project to the fastigial nucleus. Neurons in the fastigial nucleus project out of the cerebellum to four main targets:

- Ventrolateral thalamus and from there to primary motor cortex to cells that give rise to the anterior corticospinal tract
- Superior colliculus to control tectospinal output
- Reticular nuclei that give rise to reticulospinal tracts
- Vestibular nuclei that give rise to vestibulospinal tracts

Through these connections, the vermis modulates postural control and axial movements, as well as orienting movements including gaze (see Chapter 26). The vermis is involved in gait as well, and lesions of the anterior vermis alter gait profoundly (see Box 24-6). Note that the output from the fastigial nucleus to the ventrolateral thalamus and superior colliculus travels through the superior cerebellar peduncle, as do the vast majority of cerebellar efferents. However, cerebellar outputs to reticular and vestibular nuclei travel through the *juxtaprestiform body*, which joins with the restiform body to form the inferior cerebellar peduncle.

THE OUTPUT OF THE PARAVERMIS TARGETS THE LATERAL CORTICOSPINAL AND RUBROSPINAL TRACTS

The output of the paravermis targets rubro- and corticospinal pathways necessary for reaching, grasping, and other movements using appendicular muscles. Purkinje cells in the cerebellar cortex of the paravermis project to the interposed nucleus, which in turn sends efferents through the superior cerebellar peduncle to synapse in:

- Ventrolateral thalamus and from there to primary motor cortex and other cortical regions where cells give rise to the lateral corticospinal tract
- Magnocellular portion of the red nucleus, which gives rise to the rubrospinal tract

Through these connections, the paravermis is particularly important to reaching and grasping movements.

CEREBELLAR LOOPS THROUGH THE VERMIS AND PARAVERMIS CONTINUALLY CHECK MOVEMENTS

Pathways through the vermis and paravermis start and end in the same place, forming a closed loop. For instance, in the case of an orienting movement initiated by tectospinal neurons, fastigial neurons project back to the superior colliculus, whence the movement command signal originated. Similarly, when a postural adjustment arises from lateral vestibulospinal tract neurons or when cells in motor cortex initiate a grasp, the output of the cerebellum reaches the vestibulospinal or motor cortical cells, either directly in the former case or indirectly via the thalamus in the latter case.

When the motor cortex, red nucleus, or reticulospinal or vestibulospinal neurons initiate a movement, efference copy from the spinal cord border cells reaches the cerebellum via mossy fibers from the spinocerebellar tracts. The Purkinje cells compare the planned movement with reafference received from mossy fibers from the dorsal spinocerebellar or cuneocerebellar tracts. Although the nature of the signal carried by climbing fibers from inferior olive cells to the cerebellum is highly controversial, climbing-fiber discharge somehow distinguishes between correct movements—target is reached, and incorrect movements—target is missed. When the end of a movement is reached and position equals intended target, the Purkinje cell is strongly activated, which in turn essentially stops all activity in the deep cerebellar neuron, thereby reducing the excitatory drive on the motor center targeted by the cerebellum, so that the movement ends. This loop through the cerebellum takes about 20 ms to complete and is happening all the time. Essentially, this loop keeps our movements smooth and coordinated and prevents movements from being ataxic.

OPEN LOOPS THROUGH THE LATERAL CEREBELLAR HEMISPHERES ARE USED TO LEARN NEW FANCY MOVEMENTS

Lateral cerebellum-mediated movements are typically fancy or skilled movements and not the movements such as walking and postural balance that we are innately destined to learn. They often require coordination between multiple limbs or between vision and movement, so-called *eye–hand coordination*. They include skilled movements, such as a fancy dance step, or motions used to play a new musical instrument or sport. As an example, consider teaching a child how to serve a tennis ball. To do this, the eventually fluid motion is initially broken up into segments: stance, toss the ball, knee bend, upswing, hit the ball, follow through. At first, each motion is practiced separately and then combined in a deliberate fashion. Practice utilizes the lateral cerebellum to recognize the proper feel of each serve component and eventually to sequence them together seamlessly. When learning is complete, the entire serve is performed without thought: it is a motor memory, and the cerebellum then simply oversees its future repetition by rote execution.

Purkinje cells in the lateral cerebellar hemispheres project to neurons of the dentate nucleus, which in turn send efferents through the superior cerebellar peduncle to terminate in:

- Ventrolateral thalamus, and from there to cells in the supplementary motor area
- Parvocellular portion of the red nucleus, which in turn projects to the inferior olive nuclei, the source of climbing fibers

The lateral hemispheres are critically involved in coordinating movements under visual or other mental guidance. Yet, curiously, individuals can withstand large lesions of the lateral cerebellar hemispheres with little motor dysfunction. Ataxia is not typically seen after damage to the lateral hemispheres. Thus, it may be that the lateral hemispheres contribute more to learning new skilled movements than to correctly making previously learned ones.

THE CEREBELLUM MAY ALSO MODULATE NONMOTOR FUNCTIONS INCLUDING COGNITION, AFFECT, AND HOMEOSTASIS

Language, cognition, affect, and visceral function may rely on contributions from cerebellar circuits. This still-controversial idea follows naturally from the neuroanatomy: most parts of the cerebral cortex, including nonmotor areas, project into the cerebellar cortex, via the pontine nuclei. Each cerebellar region projects back, via the thalamus, to either motor or prefrontal cortex, where input can presumably influence movement in a direct or indirect fashion. Thus, it appears that the nonmotor deficits occasioned by cerebellar lesions are those supported by the portion of cortex from which that part of cerebellum receives input but that the read-out for these deficits are motor. Although nonmotor problems resulting from cerebellar injury or disease are typically overshadowed by obvious ataxic and dysmetric movements, deficits in language, cognition, affect, and visceral function are documented in patients with cerebellar lesions. One important consideration in evaluating these reports is whether damage has occurred elsewhere in the brain in addition to the cerebellum. Nonetheless, some of the potential nonmotor roles for the cerebellum that have been proposed include:

- Input from the temporal lobe of the dominant hemisphere, critical to **language**, reaches the contralateral posterolateral cerebellum, a region within the territory of the posterior inferior cerebellar artery (see Chapter 14). During language tasks, this part of the cerebellum is active. Further, lesions of this area, typically due to a posterior inferior cerebellar artery (PICA) stroke, produce difficulties in language that are well beyond those expected by motor difficulties in speech and articulation. Patients with such lesions speak fluently, can repeat sentences normally, but are poor at generating words (e.g., name as many animals or colors or places as you can in 1 minute),

finding similarities between two words (red and blue are both colors), or generating antonyms (tall is the opposite of short).

- Prefrontal cortex, critical to so many functions that make us “human,” forms a loop with the posterior lateral lobes and the dentate nucleus. This loop may be important for people to match their **behavior** and **affect** to the appropriate situation, meaning that in the absence of this function, people act inappropriately—being overly familiar with strangers, flat with loved ones, swearing in a formal situation, or joking when faced with a serious situation.
- The vermis contributes to normal **visceral function**. Through connections with the hypothalamus, the vermis influences cardiorespiratory adjustments to postural changes, exercise, and stimuli that elicit fear.

Since the microarchitecture of the entire cerebellum is the same, the processing transform imposed upon nonmotor inputs is likely to be the same as that imposed by the vermis, paravermis and rostral portions of the lateral lobes upon motor inputs. If you imagine cerebellar processing as a set of gears (would it be so simple), then motor and nonmotor information alike are changed or transformed by similar sets of gears. While we do not yet enjoy a deep understanding of the “cognitive transform” or the “language transform,” the deficits suffered by patients with cerebellar lesions suggests that the cerebellum may process virtually every brain function. This idea is further supported by modern imaging studies showing activation of cerebellar neurons in a wide variety of language, reasoning, affective, and behavioral tasks.

There are many speculative ideas regarding what the cerebellum contributes to nonmotor function but this remains an open and very important, as well as controversial, area of investigation. The answer must conform to the following principles:

- The cerebellum is an associative learning specialist, using data to rapidly adapt brain function to changing conditions.
- The cerebellum receives an enormous amount of sensory information about the outside world and the body’s internal state.
- The cerebellum receives an enormous amount of information from cortex about ongoing activities—movements, thoughts, mood.
- When functioning properly, the cerebellum modulates function in advance, in a feed-forward manner, guaranteeing proper function and preventing mistakes before they occur.

One speculative idea is that our “automatic” reactions—be they motor, affective, cognitive, or linguistic—are elicited by familiar situations, situations that have occurred countless times before. The cerebellum may associate a particular output—movement, feeling, thought, or language—to a particular set of internal and external stimuli. Just as one learns to smoothly serve a tennis ball or play a piano recital, one can presumably learn a cognitive strategy for solving a problem, constructing sentences, making instant judgments about people, evaluating the power structure in a group, or assessing one’s safety.



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¹ Note that the word cerebellum is not mentioned in *Blink*. Yet, one may speculate that the unconscious and quick judgments discussed in this thought-provoking book could arguably employ cerebellar function.

CHAPTER 25

BASAL GANGLIA: ACTION SELECTION

The striatum and pallidum are the core participants in circuits that adapt behavioral output to conditions with continually changing priorities and dangers. As introduced in Chapter 13, functional and connectional considerations have led to grouping forebrain and midbrain nuclei—the substantia nigra pars compacta, substantia nigra pars reticulata, and the subthalamic nucleus—together with the striatum and globus pallidus as the basal ganglia. These regions operate via parallel but interacting loops with the cortex and brainstem to influence motor, oculomotor, motivational, emotional, and cognitive components of behavior. This chapter focuses on circuits through the dorsal striatum that contribute to skeletomotor action selection. The basal ganglia's contributions to the function of the oculomotor system are discussed in Chapter 26.

Although they are intimately involved in motor function, the basal ganglia exert their effects indirectly through projections to motor control centers of the brainstem and even more indirectly through projections, via thalamus, to cortex, primarily motor and prefrontal cortices. Targets of basal ganglia output in turn control the motivation, affect, strategy, and initiation of self-generated actions.

THE CORE FUNCTION OF THE BASAL GANGLIA IS TO CHOOSE BETWEEN MUTUALLY EXCLUSIVE ACTIONS

The striatum and pallidum are phylogenetically ancient structures, with the former present in the earliest vertebrates—think hagfish—suggesting that the original, and potentially still core, function of the striatopallidal system solves a problem that all animals face. The ubiquitous and fundamental problem resolved by the basal ganglia is that actions that use the same muscles differently simply cannot occur simultaneously. A fish cannot swim to the left for food, to the right toward a mate, *and* forward to get farther away from a predator circling behind. The fish has to choose one of these actions. Similarly, we cannot turn left to go to a fruit stand, right toward a friend's apartment, and accelerate forward in case the speeding car behind does not slow down. Just as fish do, we must choose one of several, mutually exclusive actions. *In fish, reptiles, birds, and mammals, including humans, striatopallidal circuits select and promote one action*

NEUROPSYCHIATRIC DISORDERS CAN BE VIEWED AS PROBLEMS OF ACTION SELECTION.

Several neuropsychiatric disorders can be understood as problems of action selection. Action selection breaks down when a person stays with an action beyond the point of that action's usefulness, a process termed **perseveration**. **Obsessive-compulsive** behavior represents perseverative action. A person who compulsively washes her hands until they are raw and bleeding perseverates, unable to select another action even though the hand-washing no longer serves a hygienic purpose. Alternatively, a person may not stick with an action long enough to derive full benefit. **Attention-deficit hyperactivity disorder** exemplifies this type of problem in which a child flits from one action to another or one focus to another. Motor disorders such as **Tourette syndrome** involve excess movements and may result from incomplete suppression, so that inappropriate, random movements break through the basal ganglia's suppressive blanket and interrupt appropriately selected actions. Basal ganglia dysfunction has been implicated in all of the above-mentioned disorders.

while suppressing competing actions. The process of choosing one action from many possible ones is termed **action selection** (see Box 25-1).

Although organized similarly in animals throughout the vertebrate tree, neurons and circuits of the basal ganglia achieve far greater complexity and vastly more connections in the cerebral cortex of mammals and especially in humans. The increase in basal ganglia complexity from fish to human reflects:

- A much more complex body plan. Humans control limb, digit, laryngeal, and facial muscles that fish, sharks, and snakes do not possess.
- More complex interactions with gravity and the physical environment on land than in sea.
- A larger behavioral repertoire. Fish swim this way and that, whereas humans swim, crawl, walk, hop, run, jump, and skip as well as play guitar, yodel, and so on.
- An enormously complex social structure, in which individuals tailor their actions to specific persons or people. A child shares her favorite toy with a best friend but not with a stranger.
- The ability to learn from experience and match behavior to particular circumstances. An infant goes to pet the friendly cocker spaniel and unfamiliar pit bull alike whereas after acquiring some experience with dogs, she pets the friendly cocker spaniel and even the familiar pit bull, but walks away, hands in pockets, from the unfamiliar pit bull.

Humans not only face more options when considering what to do at any one time than do fish but they also consider far more variables in making the decision than do fish. Nonetheless, the fundamental challenge of **choosing** between available options is the same whether one faces two or a thousand options, and therefore the same basic neuroarchitectural solution to the action selection problem works in hagfish, lizards, sparrows, elephants, and humans.

THE BRAIN LIMITS THE ACTIONS WE CAN PERFORM SIMULTANEOUSLY EVEN WHEN CANDIDATE ACTIONS DO NOT UTILIZE THE SAME MUSCLES

Basal ganglia circuits choose an action from among the candidate actions possible for any given muscle. They then control how long an action continues, whether a different action is of sufficient urgency to interrupt the current ongoing action, and when to end an action. The basal ganglia even exert limits on our ability to move beyond the absolute constraints imposed by a finite set of muscles. In Chapter 1, you appreciated the basal ganglia's limitations on movements by trying to simultaneously pat your head, rub your stomach, move

your foot back and forth, and count up by sevens (Fig. 1-6). Everyone can easily perform each of the component actions alone but far fewer can perform all actions together. There is no *physical* reason why these actions cannot occur at the same time. *The only obstacle to multiple simultaneous actions arises from the “chooser” within brain, the basal ganglia.*

Consider a clerk at the grocery store. As the clerk scans through one customer's items, a shopper asks, “Where could I find chicken broth?” Clerks, particularly novices, typically stop scanning items as they look up, think for a moment, and then tell the shopper the number of the aisle that contains soups and broths. Yet, *continuing to scan grocery items while answering a question presents no true motoric challenge*. In other words, moving items past a scanner and speaking are both easy movements and since they employ non-overlapping musculature, nothing physical prevents the two movements from occurring simultaneously. Only because of the basal ganglia's influence do the two nonconflicting movements not occur together.

OUR DEFAULT CONDITION IS TO DO NOTHING

At rest, the basal ganglia suppress all movement, so that not moving is our default condition. One can think of the basal ganglia as one large wet blanket, greatly hindering movement—or thought or emotion—until and unless the importance of an action reaches a critical level. When a candidate action becomes imperative, the basal ganglia release only the imperative action from suppression while maintaining the wet blanket over all other, mutually exclusive actions.

Determining which action to allow out from under the basal ganglia's suppressive clamp depends on the circumstances. The action, judged most salient based on present conditions and past experiences, wins the competition, and the basal ganglia release this action from inhibition. Other potential actions, losing competitors to the winning action, remain suppressed by the basal ganglia. If circumstances change and a different action becomes sufficiently imperative, the basal ganglia interrupt the current action and release the newly imperative action from inhibition. As we move through the world, the basal ganglia paces and sequences particular actions to fit with external conditions, our own judgments of urgency, and lessons learned from past actions.

GROUPING TOGETHER OFTEN REPEATED MOVEMENTS ENABLES SIMULTANEOUS ACTIONS

The basal ganglia repeatedly select actions or series of movements with positive outcomes. When such a series of movements is selected over and over again, occurring in sequence time after time, the basal ganglia group

those related movements together. **Chunking** of related and often repeated movements enables a series of movements to be relatively hard-wired together. Thus, *chunking permits a sequence of movements to occur without the need for selecting each component movement* (see Box 25-2). For example, when you see a face, you move your eyes to focus on the eyes, mouth, hair, and so on in order to identify the person. Grouping together all the movements needed to scan a face for identification simplifies what would otherwise be a very complex set of movements. Once learned, chunked behavior can easily be chunked with other behaviors. An experienced driver—one who has essentially chunked all of driving into one automatic action—may be able to change the radio station while on the expressway. In contrast, a student driver who still performs each component movement of driving individually finds it challenging to add the simple movements involved in changing the radio station to the multitude of component driving movements not yet grouped together within a chunk.

The grouping of a series of movements into a single action allows us to wash our hands, brush our teeth, dial a phone number, or type a word on a computer as though it were a single action instead of a long sequence of individual movements. Even though it requires more movements to retype a simple word such as “that” than it does to fix one letter in a misspelled version such as “thet,” the former is more quickly accomplished because it can be performed as a chunk whereas the latter requires deliberate focused action.

Along with the advantages of chunking comes a disadvantage—once started, a chunk is difficult to interrupt. Once you start signing your name, it requires deliberate effort to stop in the middle. The difficulty in interrupting a chunk stems in part from

Box 25-2

CHUNKING EXTENDS OUR CAPACITY TO MAKE MULTIPLE SIMULTANEOUS MOVEMENTS.

Because of the fundamental limitations of short term memory, we have a progressively harder time remembering an increasing number of items. More than about seven items overloads the typical person’s short term memory. Packaging items together into **chunks** provides a solution. Thus, instead of remembering your best friend’s telephone number as seven separate numbers, you store and retrieve it—or fail to recall it—as a single piece of information. Now, consider motor versions of chunking (also called **habits**): opening a door, typing “t-h-e,” or signing your name. In opening a door, a person grips the door knob, turns the door knob, pushes on the door knob, holds the door knob while walking over the threshold, and finally releases the door knob. Rather than consciously drawing each line segment within a signature, an adult starts and

completes a signature in one action. *The reduction of an intrinsically complicated series of movements into one action is the essential advantage of chunking.* Many of the chunks typical of daily life—washing, grooming, eating, checking that appliances are off before going out—are replayed, repeatedly, by people suffering from obsessive-compulsive disorder. People with obsessive-compulsive disorder feel compelled to perform a chunk such as washing hands, from its beginning and in its entirety. The disadvantage of chunking is that automated sequences are freed from contingencies; they continue whether useful, neutral, or even harmful. Thus, obsessive-compulsive patients replay the same chunk over and over again, even though it serves no purpose and in many cases, is debilitating.

the independence of that chunk from its outcome. In other words, we complete chunks regardless of whether they produce positive, neutral or negative results. *Freeing chunks from contingencies enables us to easily perform complicated movements without focused thought and attention and allows people to achieve many of their goals automatically. However, dissociating actions from resulting outcomes also promotes completion of acts that may not always serve us well.*

The aggregation of basic chunks into more and more complicated chunks enables the assembly of complex behaviors. For example, washing hands forms one of the building blocks and combines with washing hair and many other washing and drying chunks to automate taking a shower. Such layered chunking allows action selection to work on loftier choices than would be possible in the absence of chunking. Thus, one chooses between taking a shower and fixing breakfast rather than between supination and pronation of the wrist. In sum, we perform many, if not most, of our daily activities by initiating packages of motor behavior, initially formed into chunks by the basal ganglia.

Now consider a clerk who has worked at a store for many years. After endless repetition, the clerk likely has grouped the movements involved in scanning items into one chunk. Now, when asked a question, the clerk can easily continue to scan items while answering the customer's question because scanning items is one action rather than a multitude of motions, as it is for a clerk new to the job. Thus, *the basal ganglia allow multitasking only when all but one task are performed by habit as chunks, freeing cortex to initiate nonroutine actions.* When sufficient need or urgency arises, rote execution of a chunk is interrupted to support a "single-minded" action.

PATHWAYS THROUGH THE BASAL GANGLIA EMPLOY THE SAME INPUT AND OUTPUT PORTS

Circuits resulting in action selection and chunking follow common pathways through the basal ganglia, which we explore in some detail here. In general, the basal ganglia process input from one area and return their verdict—the product of all their processing—to the same and related, nearby areas. These loops through the basal ganglia moderate between competing candidate actions—or thoughts or emotions—and then release the winning candidate from inhibition while ensuring that the losing candidates remain suppressed.

The architecture of basal ganglia loops is stereotyped across the different loops. At its root, the architecture is quite simple involving two regions that receive input and two regions that project out of the basal ganglia to target structures (see Fig. 13-14). Afferents from outside of the basal ganglia project into and excite neurons in:

- Striatum
- Subthalamic nucleus

The output from the basal ganglia is carried by neurons in:

- Substantia nigra pars reticulata
- Internal globus pallidus

Additional features characteristic of basal ganglia loops make them ideally suited to selection regardless of whether the thing being selected is an action, thought, strategy, or emotion. First, *the number of inputs to the basal ganglia far outnumbers the outputs*. This allows all candidates access to the selector—the basal ganglia—while also maintaining the basal ganglia's selection-making authority. One can think of the basal ganglia as akin to the director of a drama who entertains as many hopeful actors as care to audition but chooses only one to play a part. Furthermore, the default state is that none of the candidates is selected, just as none of the actors has the part prior to auditions. The basal ganglia maintain this default state through tonic GABAergic inhibitory output, provided by neurons in the internal globus pallidus and the substantia nigra pars reticulata, to all target structures.

More than 90% of the neurons in the striatum are GABAergic neurons of medium size with spine-covered dendrites; these cells are called **medium spiny neurons**. Input to the striatum converges on medium spiny neurons. In the case of skeleto- and oculomotor loops through the basal ganglia, regions within motor control centers that influence movement of a specific body part converge on medium spiny neurons within a localized region of the striatum. For example, both frontal eye fields and superior colliculus, cortical and subcortical sites that control eye movements, project into the caudate, whereas medial parts of motor cortex project to the leg region of the putamen, which also receives input from the subcortical *mesencephalic locomotor region*.

Although allowing an open and full competition between synaptic inputs, the basal ganglia, like the director of a play choosing the actor for a part, selects only one winner from the candidates bidding for control of each resource; the resource can be particular muscles, thought, attention, motivation, or emotion. Selection takes the form of a focal relief of the inhibition exerted on the winning input. For example, the basal ganglia may release from inhibition a saccade, a ballistic eye movement, toward the door while continuing to suppress saccades to other locations.

Cortical and subcortical sites connect with the basal ganglia through different routes (Fig. 25-1). Cortical regions project directly into the basal ganglia but receive output from the basal ganglia only indirectly via the thalamus. In contrast, subcortical regions, such as the superior colliculus and the mesencephalic locomotor region, project indirectly, via the thalamus (see Box 25-3), to the basal ganglia but receive the output of the basal ganglia directly. In a head-to-head competition, *subcortical inputs enjoy an advantage over cortical ones as the former synapse on striatal neurons more proximally and more densely than do the latter*. As discussed below, this advantage promotes subcortical goals such as orienting toward a streaker unexpectedly running across the front of the lecture hall—a movement mediated by the superior colliculus—over continuing to orient toward the lecturer—an action mediated by frontal eye fields. Indeed, most people would find *not glancing at the streaker* a most difficult task.

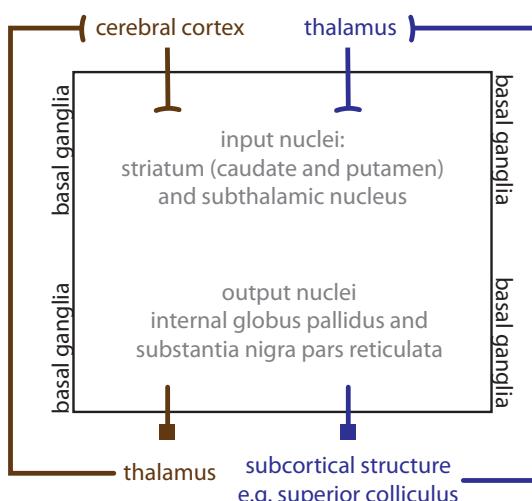


Figure 25-1. Cortical loops (brown on left) involve direct projections to the basal ganglia coupled with indirect projections, via thalamus, from basal ganglia back to cortex. In contrast, subcortical structures reach the basal ganglia only through a synapse in thalamus but receive output from the basal ganglia directly (blue on right).

Box 25-3

THE PATHWAY FROM SUBCORTICAL STRUCTURES TO STRIATUM IS INDIRECT VIA THE INTRALAMINAR NUCLEI.

Subcortical sites such as the superior colliculus project indirectly to the striatum via the thalamus. Much of the input from superior colliculus to striatum follows a pathway through the **intralaminar nuclei** of the thalamus. The intralaminar nuclei are a group of about a dozen small thalamic nuclei with diverse functions and located near the midline. This heterogeneous group of nuclei has often been termed *nonspecific*, which is certainly true in comparison with a thalamic nucleus, such as the lateral geniculate nucleus, which specifically serves a visual function. However the term nonspecific probably reflects more upon our ignorance than upon the true nature of intralaminar nuclear function. Recent attention to the intralaminar nuclei has resulted in proposed roles in attention, visual processing and other cognitive tasks: limbic, visceral and sensory. One possibility is the overarching view that the intralaminar nuclei link attention and arousal to cognitive, motor, limbic, and sensory inputs. The common theme here is that the intralaminar nuclei as a group facilitate arousal and attention and that different intralaminar nuclei target different processes with attention. Understanding the intralaminar nuclei is certainly a work in progress and an exciting challenge for future investigators.

THE SKELETOMOTOR LOOP EMPLOYS EFFERENCE COPY, AND SENSORY AND COGNITIVE INFORMATION TO ACHIEVE ACTION SELECTION

The basal ganglia influence actions using skeletal muscles through the *skeletomotor loop*. The notable exception to this rule is that eye movements are modulated by the oculomotor loop of the basal ganglia. In this chapter, we focus on the skeletomotor loop through the basal ganglia before briefly discussing loops through the basal ganglia that influence cognitive and emotional function.

In order to select an action, the basal ganglia utilize information of three major types:

- *Efference copy* that provides a running record of current and imminent actions, as well as those in the immediate past (see Chapter 24 for a refresher on efference copy if needed)
- *Sensory, cognitive, and affective information* that convey the current internal and external circumstances, as well as memories associated with those circumstances
- *Urgency or importance of different actions*, including the action being currently performed

Efference copy from currently selected actions heavily biases basal ganglia selection. Thus, *without a compelling reason to stop, we typically continue doing what we are currently doing*. A person reading the newspaper at 7:23 is astronomically more likely to be reading the newspaper than to be doing sit-ups or any other action besides newspaper-reading at 7:24. In this way, efference copy allows for *behavioral continuity* in our actions, lending great advantage to the current action over any other potential action. Of course, behavioral continuity also supports biological inertia, favoring the continuation of ongoing activity, or inactivity as the case may be, for hours. In this regard, think of the great effort needed to start an activity, such as writing a term paper, in contrast to our ready ability to while away an entire afternoon “doing nothing.” When a selected action is completed—the newspaper has been read—efference copy stops and basal ganglia selection is once again an open competition. *By biasing action selection heavily toward the currently selected action, efference copy input to the basal ganglia promotes sticking with an action for as long as it takes to complete the action while also preventing us from perseverating with an action already completed.*

Internal desires and external stimuli lend support to one action or another, tipping the basal ganglia’s ultimate “decision” toward a particular action. Consider how grocery clerks would behave if, instead of working 8-hour shifts, they worked 1,000-scan shifts; viz, the clerk could leave work after scanning 1,000 items regardless of whether this took 2 or 12 hours. One can imagine that working under

this regime, many more clerks would quickly train themselves to group scanning items into a chunk. Most people are far more likely to go bike-riding on a sunny day than on a rainy one, when their legs feel strong rather than when experiencing muscle cramps. People are more likely to exercise on January 2, propelled by New Year's resolve, than just a few days earlier in late December. We pick fights when angry or frustrated much more often than when we are happy or even sad. In sum, the solution to every instance of action selection—should I do a somersault, lift weights, or play with my cat?—depends on internal and external sensations, cognition, and affect.

OPERATIONAL LEARNING PROVIDES CRITERIA WITH WHICH TO CHOOSE BETWEEN ACTIONS

Every candidate action offers different advantages and disadvantages. To choose between candidate actions, action selection uses criteria, preferably criteria that serve an organism's survival needs. The selection criteria employed by the basal ganglia are based on *operational learning*, an unconscious associative process continuously executed by the basal ganglia (see Box 25-4). Operational learning is the process by which we learn to associate our actions with the consequences of our actions. Rules learned through operational learning become the criteria and provide the evaluative structure that allows for selection between potential actions. When a visitor pushes a doorbell, a sound emanates from within the dwelling. When this first happens to a child, the *ding-dong* is unexpected. However, after learning this operational rule, the only unexpected outcome would be *not* hearing a sound after pressing a doorbell. One controversial idea posits that a phasic burst of dopamine release accompanies unexpected sensory events and facilitates the association between the preceding motor command and the resulting sensory outcome.

All predictions emerging from operational learning exist unconsciously, although some rise to conscious levels as well. Some lessons derived from operational learning are both realistic and critical to survival—pet cats learn through operational learning that if they meow loud enough, they will be fed. Other lessons derived from operational learning are more hopeful than realistic—every time I wear this shirt, my team wins. Since operational learning is neither logical nor based on thought processes, the basal ganglia do not always make wise choices that optimize benefit and minimize danger.

Via mechanisms that remain highly controversial, *operational learning biases the basal ganglia's action selection toward actions associated with returning rewards and away from actions with negative consequences*. Thus, operational learning provides subjectivity to the basal ganglia's choosing. One person, having fond memories of beach vacations, may excitedly jump into the ocean to swim and play whereas another person, remembering a past pummeling by surf, runs from every incoming wave, frightened to even wet her feet. Telling stories provides a common example of the subjective choosing performed by the basal ganglia. People tell and retell stories about meaningful events, “I was at the corner of Main and 5th when I felt the earth move...” but not of mundane happenings, “This morning, I made oatmeal...”

OPERATIONAL LEARNING LEADS TO AN ASSOCIATION BETWEEN AN ACTION AND THE SHORT-TERM CONSEQUENCES OF THAT ACTION.

Operational learning, also called **instrumental**, **procedural**, **operant**, or **reinforcement learning**, refers to an implicit type of learning in which we learn to associate self-generated actions with their effects. We use this information to bias our behavior toward actions that produce positive effects over those that cause negative effects. In this type of learning, an individual generates an action and then associates the ensuing consequences with the action. A cat meows in the morning and is fed, a child that cries is picked up and comforted, a person walks outside with bare feet and sustains a foot injury, a basketball player does not play defense and is benched. As a consequence, the cat meows every morning, the child cries when she wants attention, the person wears shoes when venturing outdoors, and the player tries to block opposing teams' shots. Thus, *actions that produce favorable outcomes recur and those that produce immediately adverse effects are rarely repeated.*

Operational learning works over a short time frame, so that the immediate consequences of an action are the only consequences of importance.

Consequences that occur some time later are not associated with our actions through operational learning. Thus, a rat who presses a lever and receives an intravenous bolus of cocaine learns to associate pressing the lever with the immediately positive feeling produced by the cocaine. Why not press the lever again and again? Indeed, rats do just that and may press a lever for a drug such as cocaine to the exclusion of eating and other critical survival behaviors. Operational learning does not take the "long view" but rather continues to favor continued lever-pressing over the wiser choice of eating, drinking, and sleeping. Many view drug abuse as a problem that is at least in part the product of operational learning. According to this view, taking drugs has been learned and is no longer constrained by any contingencies. Moreover, the extinction of operational learning is slow. How many days would you have to ignore a cat's meow or a baby's cry before the cat or the baby would stop trying to get your attention by meowing or crying? An individual who wants to unlearn the ultimately counterproductive behavior of drug abuse faces a difficult biological obstacle.

Weighty actions—talking about a momentous event, running from perceived danger, eating when hungry—win the basal ganglia's attention far more often than do banal, tedious ones. The basal ganglia deem particular actions inconsequential, preferred, or imperative by the degree to which they release circuits supporting each particular candidate action from inhibition. *In sum, memories and associations formed by operational learning, more so than sensory details, tip the scales for or against candidate actions.*

THE SKELETONOMOTOR LOOP INCLUDES SEVERAL INTERACTING CIRCUITS

Remember that motor control regions that influence movement of a specific body part all project to a localized region of the striatum, within the putamen in the case of the skeletomotor loop. For example, in the oral region of the putamen, neurons might receive inputs from various cortical regions involved in generating a smile of enjoyment, a smile used for greeting, whistling, and kissing,

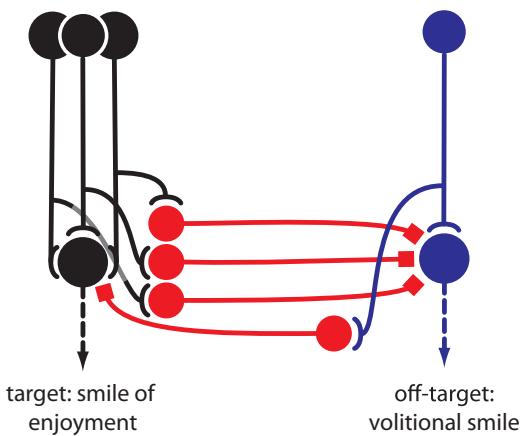


Figure 25-2. A cartoon of lateral inhibition in the striatum is illustrated. Indecision could result if striatal cells supporting two candidate actions receive similar levels of excitation. To decrease the likelihood of indecision, lateral inhibitory circuits facilitate the winning margin between the leading candidate and the runner-up. Incoming excitatory input excites target striatal cells, leading to a smile of enjoyment (*black pathway*). The same cortical cells indirectly inhibit, via local inhibitory interneurons (*red cells*), off-target striatal cells favoring a volitional smile (*blue pathway*). The result is that the close competition between the two inputs becomes a landslide victory for the target cells.

all actions that require mouth muscles. As should be clear by now, only one of the mouth movements listed can occur at a time, and the basal ganglia select the winner.

Three major pathways loop through the basal ganglia, arbitrating between all potential movements to choose one action. I list the three pathways here with their general function in action selection; subsequent sections describe each pathway in more detail:

- The **hyperdirect pathway** through the subthalamus stops current movements immediately.
- The **direct pathway** through the putamen and internal globus pallidus releases a selected movement from suppression.
- **Indirect pathways** through the putamen, subthalamus, and globus pallidus exert mixed effects, the most dominant of which suppresses competing, nonselected movements.

In addition to these three pathways, local circuits are instrumental in shaping the final output of the basal ganglia. Local circuits within the striatum, internal globus pallidus, and substantia nigra pars reticulata use lateral inhibition to facilitate the bids of leading candidates while inhibiting loser candidate actions—the neural equivalent of jumping off the sinking ship to get on the bandwagon (Fig. 25-2). Lateral inhibition hones the decision between candidate actions. For example, imagine a group of striatal cells that receive slightly more action potentials from a cortical region supporting a smile of enjoyment than the number of action potentials received by a neighboring ensemble of striatal cells from a cortical region supporting a volitional smile for the camera. Lateral inhibition will augment the activity of the former cells at the expense of the latter ensemble, enlarging the margin between winner and loser. Thus, *lateral inhibition opposes indecision in action selection, preventing us and other animals from spending unproductive time deciding between candidate actions of nearly equal weights*.

Recall that neurons in the substantia nigra pars compacta are dopaminergic neurons that project to the caudate and putamen as the *nigrostriatal dopamine pathway*. Centered on the midline of the midbrain, between the left and right substantia nigra, is the **ventral tegmental area** that contains another group of dopaminergic cells. Dopaminergic cells in the ventral tegmental area supply dopamine to the *nucleus accumbens*, which forms the rostral pole of the striatum. Dopamine arising from the ventral tegmental area is released in the nucleus accumbens. This release is thought to be a critically important to drug-seeking behavior, as many drugs of abuse, as well as fast-paced video games, result in dopamine release in the nucleus accumbens.

The nigrostriatal dopamine pathway from substantia nigra pars compacta to the striatum is critically important to movement. Dopaminergic nigral cells densely innervate the striatum, firing tonically all the time. The *tonic release of dopamine within the striatum is necessary for movement just as oil is required for an engine to run*. Moreover, dopamine strongly promotes movement in a graded fashion: more dopamine promotes more movement (see Box 25-5). The facilitation of movement by dopamine stems, at least in part, from a facilitation of the direct pathway and an inhibition of the indirect pathway (Fig. 25-3).

In addition to tonic firing, dopaminergic cells fire with a phasic burst of activity when something unexpected—a sound, a light, touch and so on—occurs. This phasic burst of activity plays an important, and highly debated, role in basal ganglia learning. For our purposes here, it is important to recognize that (1) dopamine is absolutely required for goal-directed movements, and (2) dopamine facilitates the learning of motor sequences as chunks, as well as the modification of those chunks according to changing circumstances.

THE HYPERDIRECT PATHWAY OPPOSES MOVEMENTS

Although input from motor cortex reaches both the striatum and the subthalamicus, it travels at high speed through myelinated axons to the subthalamic nucleus but courses slowly through unmyelinated axons to the striatum.

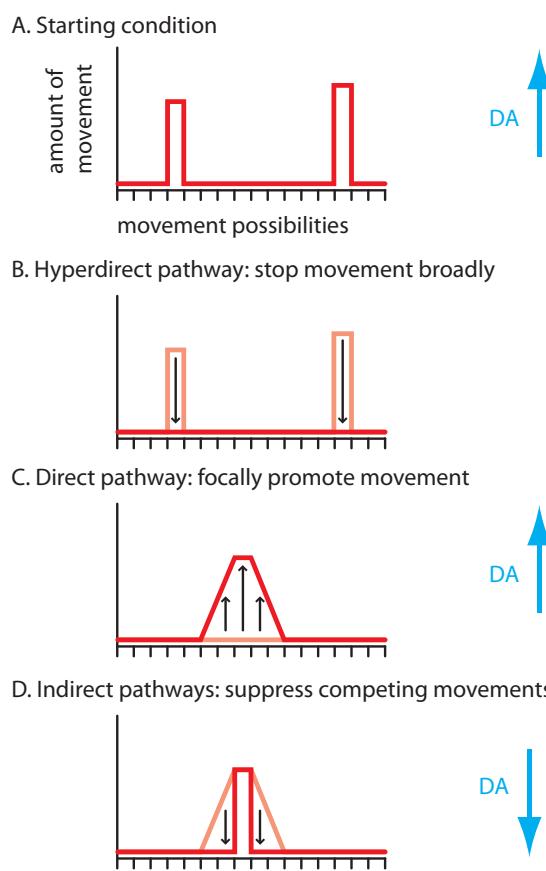
Box 25-5

DOPAMINE SERVES AS MOTOR OIL TO THE BASAL GANGLIA'S ENGINE.

Mice with a complete absence of dopamine do not move around, do not feed, and die within a day or so of birth. Although these mice do not explore or feed, they do breathe. Thus, dopamine affects certain movements but not others. *Movements requiring dopamine and the basal ganglia can be described as goal-directed*. The effect of dopamine on movement is graded. People who lose more than 80%–90% of their dopaminergic nigral cells move far less frequently than is normal, the cardinal sign of *Parkinson's disease*. Moving less than normal is termed hypokinesia, whereas a person who stops moving altogether, becoming "frozen," exhibits akinesia. Treatment with the dopamine precursor, L-dopa, increases dopamine levels (see Chapter 7) and facilitates basal ganglia-mediated movement in both dopamine-deficient mice and parkinsonian patients. *Just as a lack of dopamine causes akinesia,*

surplus dopamine causes excess movements. As a consequence, drugs that artificially increase the tonic level of dopamine, such as amphetamines or cocaine, greatly increase motor activity. Users appear jumpy and, because of this excess motor activity, are readily perceived as being "on something." In the same vein, conditions that augment dopaminergic transmission also cause excess movements. After receiving long-term treatment with dopamine receptor antagonists commonly used to treat psychiatric diseases, patients develop receptor supersensitivity to dopamine that operationally facilitates dopaminergic transmission. As a result, these patients develop an *iatrogenic*, meaning unintentionally caused by medical treatment, disorder called **tardive dyskinesia**, in which the patient makes excess movements particularly of facial and tongue musculature.

Figure 25-3. A functional overview of basal ganglia pathways is illustrated. In each graph, the amount of movement (y axis) for a number of discrete movement possibilities (x axis) is plotted. In the starting condition (A), two movements are in progress. Movements that occur simultaneously are typically both well practiced and use different muscles, for example, walking and chewing gum. When a high-priority movement arises, the first pathway engaged is the hyperdirect pathway (B). The effect of the hyperdirect pathway is to quickly stop movements in process. Immediately following the hyperdirect pathway, the direct pathway is engaged (C), leading to the focal disinhibition of a salient action. This disinhibition may not be perfectly focused on the chosen action. Indirect pathways provide an annulus, or donut, of inhibition around the chosen action (D). Thus, the indirect pathways sharpen the disinhibition produced by the direct pathway and also keep other potential movements from occurring. Dopamine (DA) facilitates (upward blue arrow) ongoing movements. More dopamine means more movement, and less dopamine means less movement. In part, dopamine's facilitation of movement stems from a facilitation of the direct pathway and a net inhibition (downward blue arrow) of the indirect pathways.



Therefore, cortex excites the subthalamic nucleus *before* it reaches striatum. Subthalamic neurons are glutamatergic, the only glutamatergic neurons within the basal ganglia, and provide excitatory drive to target cells. Once excited by cortical input, subthalamic neurons excite internal globus pallidus neurons which, in turn, inhibit neurons in the ventral anterior and ventral lateral nuclei of the thalamus, regions involved in motor control that project back to motor cortex (Fig. 25-4). This hyperdirect pathway comprises the quickest route through the basal ganglia. It increases the inhibition of target nuclei beyond that provided by the pallidal neurons' tonic discharge and thereby decreases discharge in target thalamic cells.

Activity in the hyperdirect pathway opposes action, perhaps providing an interrupt signal. If so, such an interrupt signal would be useful during:

- *Action interrupt*: stop what you are doing because something else, really important, has suddenly come up.
- *Action start*: starting a movement from a state of not-moving is far easier than switching from one movement to another. For example, if you see Betty and mistake her for her twin Beatrice, it is easier to stop saying “Beatrice” and say “Betty” than it is to switch mid-stream from “Beatrice” to “Betty.”

The hyperdirect pathway may contribute to either or both of the above functions. In either case, it appears that the net effect of the hyperdirect pathway is to oppose

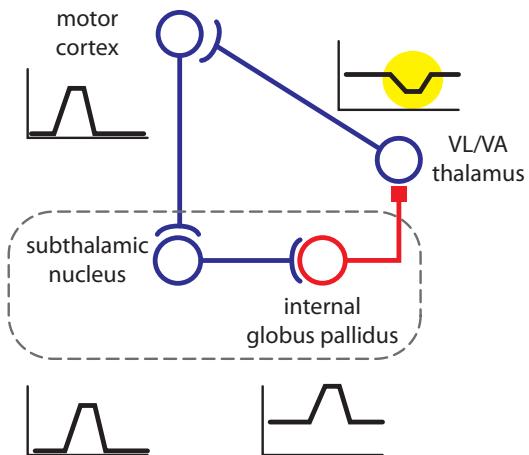


Figure 25-4. The hyperdirect pathway within the skeletomotor circuit is illustrated. Next to each neuron is a cartoon showing the firing activity in that neuron. Neurons in somatomotor cortex are normally inactive but discharge before initiating a movement. The myelinated axons of motor cortex neurons excite neurons in the subthalamic nucleus at short latency. Excitation of subthalamic neurons in turn causes an increase in the discharge of tonically active neurons in the internal globus pallidus. GABAergic cells in the internal globus pallidus inhibit the tonically active neurons in ventral anterior (VA) and ventral lateral (VL) thalamus. Since thalamic cells project to somatomotor cortex, the inhibitory effect of the hyperdirect pathway on thalamic firing (yellow highlight) is passed on to motor cortex. Thus, we can use thalamic firing as a proxy for the effect of basal ganglia circuits. In sum, the hyperdirect pathway has an immediate but short-lasting effect of widespread suppression of motor cortex. GABAergic neurons are shown in red, and their inhibitory terminals are shown as red squares. Excitatory neurons are shown in blue.

supplementary motor and premotor areas—reaches the putamen through unmyelinated corticostriatal axons. Excitation of cells in the putamen causes an inhibition of internal globus pallidus neurons, which in turn disinhibits target cells in ventral anterior and ventral lateral thalamus (Fig. 25-6). *Through removal of the tonic inhibition of thalamic neurons, engagement of the direct pathway results in an increase in the discharge rate of thalamic neurons.* An increase in thalamic activity is passed on to motor areas, facilitating the initiation of the selected action. The net effect of the direct pathway is the activation of a focused ensemble of motor control cells. The behavioral result is that one action is released from tonic inhibition and therefore occurs.

Recall that the striatal and pallidal neurons both use γ -aminobutyric acid (GABA) to inhibit their target cells. Therefore, when placed in series, the striatal inhibition of pallidal inhibition causes disinhibition, which, as you recall from Chapter 24, has the net effect of increasing discharge rate. The direct pathway only works since pallidal cells discharge tonically, rendering them sensitive to inhibitory influences from striatum. Indeed, pallidal cells as well as cells in substantia nigra pars reticulata discharge tonically at rates of 50–100 Hz.

In the direct pathway, the striatum, internal globus pallidus, and substantia nigra pars reticulata are the only nuclei that are considered part of the basal ganglia. Therefore, when cortical input engages the direct pathway, the output of the basal ganglia *decreases*. As the basal ganglia output to thalamus is inhibitory, a decrease in basal ganglia output leads to more activity in thalamic and consequently cortical neurons, and things happen. In Parkinson's disease, the direct pathway is disinhibited and movement rarely occurs (see Box 25-7).

movement. Hyperkinetic disorders, disorders that involve excess movement, result from a variety of lesions, including ones that interrupt the hyperdirect pathway (see Box 25-6).

THE DIRECT PATHWAY RELEASES SELECTED MOVEMENTS FROM ONGOING SUPPRESSION

The direct pathway provides a fast route through the basal ganglia, second in speed only to the hyperdirect pathway. In the direct pathway, information from wide areas of sensorimotor cortex—somatosensory and primary motor cortices,

HEMIBALLISM IS A HYPERKINETIC DISORDER INVOLVING INVOLUNTARY FLAILING MOVEMENTS EMPLOYING ARM, LEG, AND FACIAL MUSCLES.

Hemiballismus or **hemiballism** is a movement disorder characterized by uncontrolled flinging, flailing or other ballistic movements of the proximal arm, leg, and often the face. With time, the movements slow and often become **choreiform**, more writhing and dance-like than flailing. Some patients present initially with **hemichorea**, meaning involuntary writhing movements on one side of the body. Hemiballism and hemichorea are considered to represent two extremes of the same disorder. In most cases, the movements remit completely within several months, either spontaneously or following short-term pharmacological treatment. Treatment is aimed at the underlying cause of the lesion, which in most cases is a focal stroke. In addition, dopamine receptor antagonists help decrease the occurrence of excess movements and therefore aid patients, particularly in the initial weeks.

Hyperglycemia secondary to diabetes mellitus is the second most common cause of hemiballism. In **hyperglycemic hemiballism**, movements are transiently present for as long as blood sugar is abnormal. The pathophysiology of this recently recognized disorder, most prevalent in individuals of East Asian origin, is unknown and worthy of study. The third most common cause of hemiballism or hemichorea is a toxoplasmosis lesion in individuals with HIV disease.

For a relatively rare disorder, hemiballismus is very well known among medical professionals. For years, hemiballism was thought to result exclusively from a lesion of the contralateral subthalamic nucleus.

Certainly, there is both clinical and experimental evidence to support the idea that a lesion of the subthalamus in a healthy individual will produce a hyperkinetic disorder. The interpretation is that, without excitatory drive from subthalamic neurons, neurons of the internal globus pallidus fire more slowly, resulting in less inhibition of thalamus. The predicted behavioral consequence of this sequence of events is an increase in movement. Essentially, hemiballism has been used for decades to teach students the role of the subthalamic nucleus in suppressing movement.

Unfortunately, this attractive teaching device can no longer be employed in good faith. It is now clear that more than 60% of patients with hemiballism have a lesion outside of the subthalamic nucleus (Fig. 25-5). Lesions that produce hemiballism are found in the putamen, thalamus or deep white matter and occasionally, about 20%–25% of cases, in the subthalamic nucleus. Does this neuro-pathological finding mean that our interpretation of subthalamic nucleus function is all wrong? Absolutely not. The idea that the subthalamus facilitates basal ganglia output and thereby depresses movements is still widely accepted. However, it is now clear that hyperkinetic disorders often result from lesions of subcortical structures besides the subthalamic nucleus. An understanding of the pathophysiology involved in these nonconventional but more representative cases of hemiballism represents an intriguing puzzle for future investigators.

INDIRECT PATHWAYS KEEP RIVAL MOVEMENTS SUPPRESSED

The indirect pathways comprise a varied group of polysynaptic routes through the basal ganglia. In the classic indirect pathway, presented as the one and only indirect pathway in many texts, cortical cells project to striatal cells

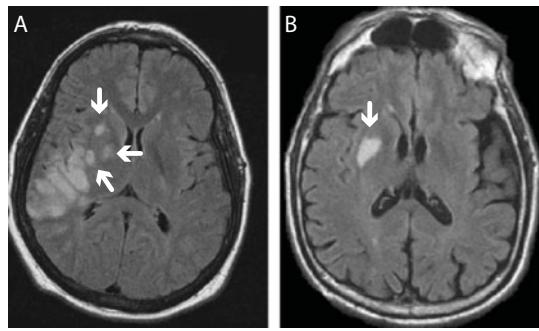


Figure 25-5. Magnetic resonance images (MRIs) from two individuals with hemiballism, neither of whom has a lesion in the subthalamus. **A:** A 34-year-old man with a stroke in the right middle cerebral artery presented with left-sided hemiballism. Affected areas include cerebral cortex and several small areas within the striatum and pallidum (arrows). **B:** A 69-year-old man with Parkinson's disease presented with left-sided hemiballism. A lesion in the right striatum (arrow) was found. The left-sided hemiballism coincided with an amelioration of this patient's symptoms of Parkinson's disease on the left side. Note that radiological convention is that the left side of the brain is illustrated on the right and right side of the brain on the left.

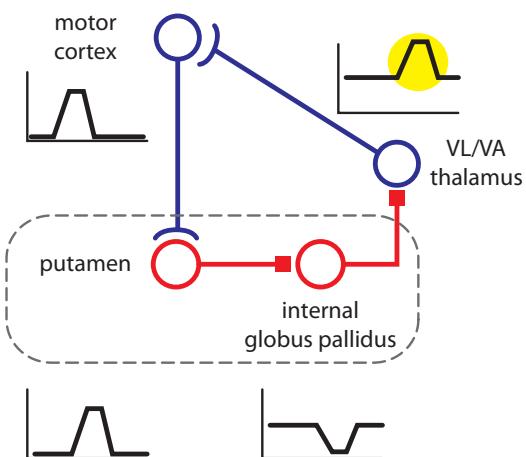
Modified from Postuma, R.B., and Lang, A.E. Hemiballism: Revisiting a classic disorder. *Lancet Neurol* 2: 661–8, 2003, with permission of the publisher, Elsevier.

that project into the external globus pallidus. External globus pallidus cells in turn inhibit subthalamic neurons, which project directly to output neurons in the internal globus pallidus.

In reality, the indirect pathway described above is only one of several possible polysynaptic basal ganglia routes (Fig. 25-7). Since all indirect pathways involve at least three synapses, they all impact basal ganglia output *after* both the hyperdirect and direct pathways. These indirect pathways offer the potential for decreasing, as well as increasing, basal ganglia output, and thereby increasing as well as decreasing motor output. Nonetheless, the overall effect of the indirect pathways appears to be a suppression of nonselected, competing movements. In Huntington's disease, initial damage is present in the indirect pathways through the basal ganglia and as a consequence, patients show an excess of movements (see Box 25-8).

Figure 25-6. The direct pathway within the skeletomotor circuit is illustrated with the same conventions as in Figure 25-4. The direct pathway starts with activity in cortical neurons possessing unmyelinated axons. A burst of activity in these motor cortex neurons excites neurons in the putamen at longer latency than is involved in the hyperdirect pathway. Neurons in the putamen are GABAergic medium spiny neurons. Therefore, a burst of activity in neurons of the putamen inhibits the discharge of tonically active neurons in the internal globus pallidus. The inhibition of GABAergic pallidal output neurons leads to a disinhibition of thalamic cells (yellow highlight). As a result, the direct pathway serves to facilitate somatomotor cortex and ultimately movement.

Modified from Chevalier, G. and Deniau, J.M. Disinhibition as a basic process in the expression of striatal functions. *Trends Neurosci* 13: 277–81, 1990, with permission of the publisher, Elsevier.



PARKINSON'S DISEASE CAN BE VIEWED AS A DISORDER OF THE DIRECT PATHWAY.

The cardinal sign of Parkinson's disease is a *poverty of movement*. The poverty of movement is specifically a deficit in initiating habitual and goal-directed movements. Most of the symptoms described for Parkinson's disease fall comfortably under the rubric of a reduction in either the number, *hypokinesia*, or speed, *bradykinesia*, of movements. There are few movements of the facial muscles, resulting in an expressionless face that is termed **masked facies**. The gait of parkinsonian individuals becomes shuffling, involving small steps with little or no clearance above the ground during the swing phase. This type of gait is termed **festinating**. The arms fail to swing normally during locomotion. Speech becomes strained, reduced in volume, and breathy. Postural stability is greatly impaired as adjustments either do not occur or occur too slowly to be effective.

There are two major symptoms beyond a poverty of movement in Parkinson's disease. First, there is **cogwheel rigidity**, which is a deficit in passive movement. When a physician tries to extend the arm of a patient with Parkinson's disease, there is resistance that gives in a ratcheting or cogwheel-like pattern. The other major symptom is a **resting tremor** of a few cycles per second. The parkinsonian tremor involves the thumb and forefinger moving as though they were rolling pills and thus has also been termed a **pill-rolling tremor**. Although perhaps the most widely known symptom of Parkinson's disease, a resting tremor is not experienced by a large number of patients with Parkinson's disease.

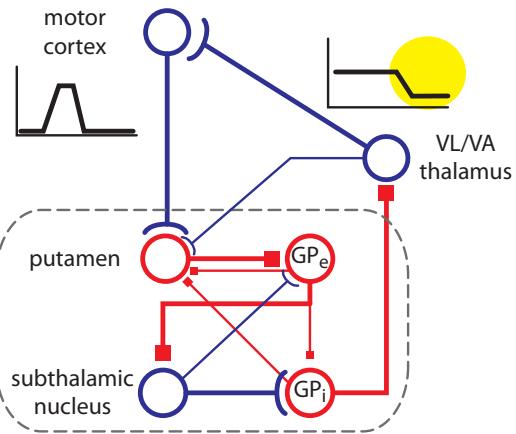
As the reader is aware by now, Parkinson's disease results after most of the dopaminergic neurons in the substantia nigra pars compacta die. The loss of dopaminergic neurons is the cause of the poverty of movement. Correspondingly, dopamine replacement remains the standard therapy for Parkinson's disease. Unfortunately, people treated with dopamine replacement over an extended period

of time often stop responding well to the treatment. In addition, patients may develop excess tic-like movements, a type of drug-induced dyskinesia. Deep brain stimulation is under active investigation as a treatment for Parkinson's disease.

There are two routes by which a loss of dopaminergic neurons could result in hypokinesia. First, as mentioned above, dopamine is necessary for movement. The exact mechanism of this absolute requirement is unclear. The second route through which a loss of dopaminergic tone could impact the initiation of movements is through dopaminergic effects on the direct and indirect pathways. The net effect of dopamine is to facilitate the direct pathway and inhibit the indirect pathways. Thus, without dopamine, the direct pathway is less excitable, and the indirect pathways are released from inhibition. The behavioral results are (1) difficulty in initiating movements due to **disfacilitation**, meaning a decrease in excitation, of the direct pathway; and (2) exuberant suppression of movements through disinhibition of indirect pathways.

Parkinson's disease is a common neurological disorder, affecting as many as 5%–10% of people over 50. Parkinson disease ranges from mild to severe. There is little chance of making it through life, and certainly through life as a physician, without encountering an individual with Parkinson's disease. Unfortunately, Parkinson's disease involves a process of progressive degeneration, and symptoms worsen over time. The development of dopamine replacement therapy in the 1960s was revolutionary as it greatly improved the lives of patients and continues to do so to this day. Nonetheless, dopamine replacement therapy is not a cure. Rather, it is an excellent therapeutic for the primary symptom of Parkinson's disease. An actual cure for Parkinson disease remains a hope for the future but is only likely to come after an understanding of why dopamine cells die is achieved.

Figure 25-7. A family of indirect pathways within the skeleotmotor circuit is illustrated with the same conventions as in Figure 25-4. Thick lines mark the conventional indirect pathway. Yet, many additional routes through the basal ganglia also exist, some of which are illustrated here in faint lines. The conventional indirect pathway involves a projection from the motor cortex to the putamen. Neurons in the putamen inhibit tonically active cells in the *external globus pallidus* (GP_e), leading to the disinhibition of subthalamic neurons. An increase in subthalamic neuronal firing excites cells in the *internal globus pallidus* (GP_i). An increase in the discharge of neurons in the *internal globus pallidus* leads to an inhibition of thalamic cells (yellow highlight). As a result, the conventional indirect pathway serves to suppress somatomotor cortex and ultimately movement. The net effect of the family of indirect pathways also appears to be net inhibition of thalamic cells and consequently a suppression of movement.



ALL BASAL GANGLIA PATHWAYS WORK TOGETHER TO ACHIEVE ACTION SELECTION

The hyperdirect, direct, and indirect pathways operate in concert to produce one action at a time and to allow for “clean” switching between actions. Here, we consider a hypothetical example. A student sits at a computer writing a term paper with a cup of hot tea and a stack of papers sitting next to the monitor. While the student could continue typing, alternative actions include ruffling through papers to check something or reaching over and drinking hot tea. Which of these three options occurs depends on action selection circuitry learned through operational learning. In the next moment, the phone rings and the cat meows. Now what does the student do? The original three options—continue typing, ruffle through papers, drink hot tea—along with two additional ones—pet the cute cat or answer the phone—are candidates. Since the options available involve different and *mutually exclusive* arm and hand movements, not all movements can occur at the same time. The basal ganglia decide the winner.

Before imagining the decision point brought on by the ringing phone and meowing cat, we consider how our student keeps writing for any stretch of time. Remember that action selection is strongly biased to the current movement. So, as long as the thoughts keep coming and the student keeps typing, typing will continue to be selected, through the direct pathway. However, when the student stops typing for a moment to think, suppression of competing movements lulls, presenting a ripe opportunity for *motor takeover* by the drink-tea or look-through-papers action plans. Within the putamen, different sets of neurons have become associated, through operational learning, with different motor chunks. One ensemble of hand-related neurons may support typing while another supports feeding (bringing things to the mouth), and another reaching and grabbing, and so on. When the student stops typing, the playing field is leveled as typing no longer enjoys the advantage of being the currently selected action. At this time, cortical neurons that could initiate tea-drinking or paper-ruffling excite neurons in the putamen associated with those two chunks. Should the excitation of putamen cells associated with ruffle-through-papers reach a higher level than the excitation on striatal neurons supporting typing, then

HUNTINGTON'S DISEASE IS A HEREDITARY DISEASE INVOLVING AN EXCESS OF CHOREIFORM MOVEMENT AND EVENTUAL DEATH.

Huntington's disease is an autosomally inherited genetic disorder with 100% penetrance. The first symptoms typically appear in the fourth or fifth decade of life. Because the mutation is dominant, patients have typically watched a parent suffer through the 10- to 20-year decline that characterizes Huntington's disease. Initially, involuntary choreiform movements are present intermittently and with time, nearly constantly. A progressive dementia develops with memory loss and eventually a nearly total loss of cognition. There is a wasting component to Huntington's disease; it is not clear whether this symptom stems from increased energy expenditure due to excess movements. With time, the excess movements subside, and individuals with Huntington's disease eventually become akinetic. On average, death occurs 15 years after diagnosis.

The genetic defect responsible for Huntington's disease was identified in 1983. Individuals with more than 40 copies of the trinucleotide repeat CAG in the *huntingtin* gene develop Huntington's disease. The onset of the disease is earliest and disease progression most rapid in patients with the greatest number of CAG repeats. The pathology of Huntington disease involves a progressive loss of neurons, starting with neurons in the caudate. The mechanism by which the mutant protein huntingtin kills

neurons remains unknown but is under active investigation.

The first neurons to die in Huntington's disease are striatal neurons that project to the external globus pallidus. Thus, neurons in the indirect pathways are affected first. This accounts for the initial hyperkinesia observed in Huntington's disease patients. More and more striatal cells and eventually pallidal and nigral cells die over time. At death, the lateral ventricles of Huntington's patients have enlarged to occupy most of the territory of the striatum and globus pallidus. As neuronal death progresses beyond the initially vulnerable population of striatal neurons that project to the external globus pallidus, hyperkinetic symptoms are replaced by progressive akinesia.

There is a genetic test for Huntington's disease but no cure. Therapy is aimed at relieving the symptoms of patients and is frankly insufficient in the face of such a relentless and debilitating disease. Consequently, a diagnosis of Huntington's disease is devastating in its promise of an inexorable decline and erosion of the life that an individual has enjoyed up until that point. The lack of either a cure or an effective treatment is often cited as the reason that the vast majority of individuals at risk for Huntington's disease have chosen not to take the available genetic test.

the direct pathway disinhibits ruffle-through-papers and the student starts to leaf through reading material. The disinhibitory effect of the direct pathway stems from one striatal ensemble supporting one motor plan. In this case, the paper-leaving chunk is released from inhibition while the tea-drinking and typing chunks are suppressed, initially by hyperdirect and subsequently by indirect pathways.

The phone's ringing and the cat's meowing present new challenges to the status quo. For many, a phone ring is hard to ignore while a cat's meow fades into the background, eliciting little response. In that case, the current action will be interrupted by the direct pathway's switch in focus to striatal cells associated with reaching and grabbing the phone receiver. If, on the other hand, caller i.d. reveals a collection agency, and the cat's meow is unusually and alarmingly plaintive, then the meow may achieve far greater saliency than the phone's ring. In this case, inputs from cortex tip striatal cells supporting cat-petting over the edge, engaging the direct pathway to

disinhibit cat-petting while other pathways maintain the suppressive clamp on all other competing actions.

To be fair, although some people may choose not to answer a ringing phone, few will be able to ignore it completely, either shifting their attention or actually orienting to look at the phone. In the scenario above, the student looks at the ringing phone to read the caller i.d. before choosing to not answer. A ringing phone or any other unexpected event commands the attention of the basal ganglia by exciting striatal cells more than anticipated stimuli. Two mechanisms support the consistent bias of action selection toward reactions to unexpected events over preplanned or anticipated inputs. First, brainstem neurons, such as those in the superior colliculus, carry inputs related to unexpected events, and subcortical excitation dominates cortical excitation of striatal cells. Second, unexpected events excite a phasic burst of activity in dopaminergic nigrostriatal cells, which in turn strengthens striatal responses to inputs. A point worth explicit consideration is the speculation that the bias toward reactions to unexpected, sudden events contributes to the short attention span prevalent in our modern world. In the natural world, rapidly paced and unexpected events are relatively rare and are noteworthy, typically signaling a potential meal or mate or an impending danger, all of which are actionable items. However, in our communication-rich world, cell phones, text messages, radio and TV news flashes all capitalize on the biological penchant to orient and pay attention to new and unexpected stimuli. These stimuli continuously invade our environment, repeatedly challenging us to switch our direct pathway focus from our current action to one that responds to the novel stimulus.

THE BASAL GANGLIA CAN LINK MOVEMENT WITH FEELING, OR ALLOW MOVEMENT TO PROCEED WITHOUT ACCOMPANYING AFFECT

The basal ganglia receive and process information about feelings, thoughts, and emotions through loops that resemble the skeletomotor loop in their *basic* architecture. All loops use some part of the striatum or the subthalamic nucleus as entry ports into the basal ganglia and either the internal globus pallidus or substantia nigra pars reticulata as the exit port. Yet, the different loops differ in terms of many specifics, such as the part of striatum, cortex or brainstem, thalamic nucleus involved. Of course, the loops also serve different functions. In addition to the skeletomotor loop, other circuits that loop through the basal ganglia and thalamus include:

- *Oculomotor circuit*: connects intralaminar thalamic nuclei, caudate, substantia nigra pars reticulata with the superior colliculus, frontal eye fields, and parietal eye fields to control gaze and orienting movements
- *Dorsolateral prefrontal circuit*: connects the head of the caudate, the substantia nigra pars reticulata, and ventral anterior and medial dorsal

nuclei of the thalamus with dorsolateral prefrontal cortex to influence executive function and cognition, such as the strategic planning of movements needed to solve a problem

- *Orbitofrontal circuit:* connects the caudate, substantia nigra pars reticulata, and medial dorsal nucleus with the orbitofrontal cortex to influence motivation and the ability to play well with others (see Box 25-9)
- *Anterior cingulate or limbic circuit:* connects the ventral striatum, including the nucleus accumbens, ventral pallidum, and medial dorsal nucleus of the thalamus with the anterior cingulum to influence emotionality and motivated-behavior

Box 25-9

NEUROPSYCHIATRIC DISORDERS MAY RESULT FROM DEFICITS IN ONE OR MORE OF THE NONMOTOR BASAL GANGLIA LOOPS.

Basal ganglia dysfunction is implicated in neuropsychiatric diseases such as obsessive compulsive disorder and *schizophrenia*. Since the basal ganglia are involved in the selection of thoughts, strategies, motivations, emotions, and goals, their heavy involvement in psychological function should come as no surprise. People with obsessive-compulsive disorder perseverate, continuing to select a single action (compulsion) or thought (obsession) over and over, long after the action or thought has outlived its utility. Patients with schizophrenia may incompletely switch between rival thoughts. If true, the simultaneous selection of multiple thoughts would result in a confusing mélange of concurrent thoughts and perceptions. The reader should also note that many, but certainly not all, patients with basal ganglia-centered movement disorders have neuropsychiatric complications. For example, nonmotor symptoms frequently afflict patients with Parkinson's disease.

Additional loops, less well characterized, also exist. One of these less well appreciated loops involves the mesencephalic locomotor region and the substantia nigra, placing locomotion and postural control within the purview of basal ganglia function. The shuffling walk and loss of postural stability in Parkinson's disease likely result from dysfunction within this loop.

Although subcortical inputs to the dorsolateral prefrontal and orbitofrontal circuits are poorly characterized and widely omitted from consideration, subcortical inputs to nonmotor circuits exist, arising from the midbrain periaqueductal gray, amygdala, and brainstem reticular nuclei. Recall that inputs originating in subcortical sites terminate more densely and more proximally on striatal medium spiny neurons than do inputs from cortex. Now, imagine that subcortical and cortical inputs excite different neuronal ensembles within the caudate territory of the orbitofrontal circuit. Chances are that the subcortically excited ensemble will win over the cortically excited ensemble, resulting in social behavior determined by noncognitive inputs. In this way, we may experience a "gut" dislike of someone for which we can not articulate a logical reason, or we may panic at the sight of a garter snake that we cognitively understand is harmless, and so on.

Loops supporting cognitive, motivational, and emotional function provide the integrated platform needed for the initiation, planning, and execution of self-generated movements. A common scenario may be that *the goal to address is selected within the limbic or orbitofrontal circuit, passed on to the dorsolateral prefrontal circuit for selection of the implementation strategy, and finally passed to the skeleto-motor loop for selection of a motor plan to execute the action*. Although the basal ganglia loops operate in parallel, information can flow from one basal ganglia loop to another through many routes involving the substantia nigra, the subthalamic nucleus, as well as through promiscuous connections from thalamus to multiple areas of cortex, and between cortical areas. As an example of the penultimate possibility, neurons in the ventral anterior nucleus of thalamus project to cortical regions that participate in loops involved in both executive function and movement execution.

Since information may, but does not always, flow between basal ganglia loops, movement can proceed with or without an associated thought or feeling. One can readily discern the difference between a phone conversation with a friend who is reading e-mail while talking to you and one with a friend focused entirely on conversing with you. To accomplish this variety of behavior, the basal

ganglia can, but does not always, couple action selection to emotions or thoughts. We can imagine that when all the loops engage in concert toward a common goal, we act “with heart.” Perhaps when only the dorsolateral prefrontal and skeleтомотор loops act in concert, we act methodically and deliberately, and when the skeleтомотор loop operates solo, we “go through the motions.” Some fully automatic acts may not need motivational or emotional support under most circumstances—a chef dices carrots at rapid speed while happily thinking about an enjoyable date the night before or an upcoming trip, a commuter drives home while thinking about the past day. However, there may be circumstances incompatible with successful completion of the same, normally automatic chunks—the same talented chef goes to work worried about a gravely ill mother and ends up cutting a finger instead of carrots, the commuter drives homeward after hearing bad news and crashes. Other actions clearly require motivational and emotional commitment for successful completion—an actor performing in a play, a parent trying to calm a child, an athlete competing in a championship game. In sum, between-loop crosstalk allows coupling of movement with emotion, intent, and focus.

THE BASAL GANGLIA AND CEREBELLUM WORK IN CONCERT

Every time that we act, the cerebellum and basal ganglia, the two great loops in the brain, receive information about the action generated from cortex. Both structures communicate indirectly with the motor hierarchy, only affecting motor neurons and motor interneurons via a circuitous route. Both structures receive at least an order of magnitude more information than they send out to target structures, making them processing bottlenecks that reduce an overwhelming confusion of conflicting input to a concise and decisive winner-takes-all output. Further the basal ganglia are critical to, and the cerebellum may influence, many nonmotor functions, processing thoughts, emotions, and memories, all of which, of course, ultimately influence movements. Even the functions of the two, in sequencing movements and learning associations, overlap.

In marked contrast to the case with the cerebellum, the basal ganglia do not receive spinal input. Instead, input to the basal ganglia comes from virtually all areas of the cerebral cortex, as well as from subcortical regions that can themselves direct movement such as the superior colliculus. Whereas some efference copy input to the cerebellum arises from spinal border cells, efference copy input to the basal ganglia comes from cortical and brainstem motor control centers exclusively. Thus, the cerebellum receives information about muscle contractions, whereas the basal ganglia only receive input about movements and actions. Sensory input to the cerebellum comes from the spinal cord and represents the sensory consequences of movement, termed *reafference*. In contrast, neurons in cortical and brainstem regions interpret and then present sensory information about the world to the basal ganglia. Consider the sequential versions of an action, from motivation and selection of a goal in prefrontal cortex to action in motor cortex, to movement in the ventral horn interneurons, and muscle control in the α -motoneurons. *The basal ganglia receive motor*

information biased toward goal selection and action whereas the cerebellum receives information biased toward movement and muscle contraction.

The cerebellum smoothes out movements, important and trivial ones alike, whereas the skeleto-motor loop of the basal ganglia ensures that salient actions take priority over automatic, mundane ones. The nonmotor functions of the cerebellum and basal ganglia may similarly diverge with the cerebellum focusing on automatisms and the basal ganglia on matching motivation, thought, emotion, strategy, and movement to urgency and circumstance.

Both the cerebellum and basal ganglia support operational learning. The cerebellum associates sensory input with motor output, so that a set of inputs related to the body and the outside world—an entire sensory gestalt—becomes associated with a particular *movement*. In contrast, the basal ganglia associate self-generated *actions* with their consequences, biasing present and future selection of actions toward previously rewarding ones. Ultimately, our actions are those dictated by the cerebellum *and* the basal ganglia, incorporating influences from the sensory world as well as from our cognitive, motivational, and emotional states.



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CHAPTER 26

GAZE CONTROL

THE DIRECTION OF GAZE IS UNIQUELY CONTROLLED

Like other mammals, we tightly control the direction of gaze. In fact, the large amount of neural territory devoted to gaze control reflects the unique importance of being able to maintain a steady gaze when so desired or change the direction of gaze when needed. There is no other body part whose position and orientation is so narrowly controlled as is the optic axis between the pupil and the fovea. Consider the hands, which are arguably very important and able to make skilled movements. Despite the obvious importance of the hands, we cannot keep them in a steady position as we do effortlessly with our gaze. For example, try reading something while exercising on a treadmill or elliptical machine. This is no problem as gaze control circuits keep our point of fixation under tight control, so that we do not see the text jumping around. In contrast, try writing while on an exercise machine: it doesn't look pretty. This difference is because of the unique control system that governs the direction of gaze.

PATTERNS OF GAZE ARE IMPORTANT FOR SOCIAL COGNITION

Like other movements, gaze control is revealing of temperament and personality. Shifty eyes effectively communicate "person with something to hide." Similarly, a steady gaze tells us that someone is honest, open, and trustworthy. Although these judgments may not always be warranted, they certainly stem from the fundamental truth that eye movements, like facial expressions and posture (see Chapter 20), are an expression of self and mood.

At a nuts-and-bolts level, eye movements dictate our perceptual reality—we can only process visual inputs from objects that we fixate upon. Furthermore, without any eye movements, visual acuity quickly degrades, and in the absence of any physical movement, the world fades from view (see Box 26-1). At a loftier level, as discussed in Chapter 15, eye movements influence our ability to accurately judge the emotional content of a person or situation (Fig. 26-1). Most people fixate primarily on the eyes and mouth of a face and determine, with high accuracy, the emotion

IMAGES THAT ARE COMPLETELY STABLE ON THE RETINA FADE FROM VIEW.

For more than a half century, we have known that without eye movements, images fade rapidly from view. Such visual fading occurs in a completely immobile person, a person without any head or eye movements. The fading of still images highlights the importance of *change* in luminance across time and space as the critical stimulus for vision. We normally avoid the fate of having the world fade from perception because we are constantly moving, even if by very small amounts. Paralysis of the extraocular muscles alone does not produce visual fading as small movements of the head are sufficient to move the visual image enough to prevent visual fading.

expressed therein. Abnormal face-scanning patterns are associated with damage to the amygdala (see Chapter 13) and with psychiatric diseases such as schizophrenia and autism spectrum disorder. Individuals who fail to scan faces normally may also fail to make emotional judgments as accurately as do control subjects (Fig. 26-1A).

Eye movements are easy to elicit, even in young children, and can be quantitatively measured. Because of these considerations, attention has focused recently on the use of eye movement abnormalities as diagnostic tools for schizophrenia and other developmental psychiatric disorders. This approach uses eye movement abnormalities as potential markers for the brain abnormalities that produce psychiatric disease. Another possibility exists, which is that eye movement abnormalities may contribute to the pathophysiology of psychiatric disease. The patient with bilateral amygdala damage described in Chapter 13 supports this idea. Recall that the patient could not detect fearful expressions until she was told to look at the eyes of a face. When she looked at the eyes, she performed normally in detecting fearful expressions. The degree to which abnormal eye movements *contribute to* or *cause* psychiatric dysfunction remains an intriguing question for the future.

EYE MOVEMENTS SERVE TO EITHER STABILIZE GAZE OR TO CHANGE THE DIRECTION OF GAZE

As the reader knows by now, gaze depends on both eye and head position (see Box 26-2). Yet, both gaze stabilization and gaze shifts depend far more on eye movements than on head movements. We therefore focus our examination of gaze control on the *oculomotor system*, a group of pathways involved in controlling extraocular muscles and therefore eye movements (see Box 16-21).

In the absence of force exerted by any extraocular muscle, passive forces place the eye in the neutral position, straight ahead (see Fig. 10-6D). Extraocular muscle contractions can deviate the globe from the neutral position to an eccentric, or off-center, position. However, in the absence of continued muscle force, the eye will relax back from any eccentric position to the neutral position. Eye movements fall into only two fundamental categories: (1) eye movements that serve to stabilize an image on the fovea at an eccentric position, and (2) eye movements that serve to shift the point of fixation.

- Three types of eye movements serve to **stabilize the fovea** on a target:
 - *Fixation* is an active process that maintains gaze in a given position.
 - The *vestibuloocular reflex* stabilizes images on the fovea during head movements.
 - The *optokinetic response* stabilizes vision during very slow or constant velocity head movements.

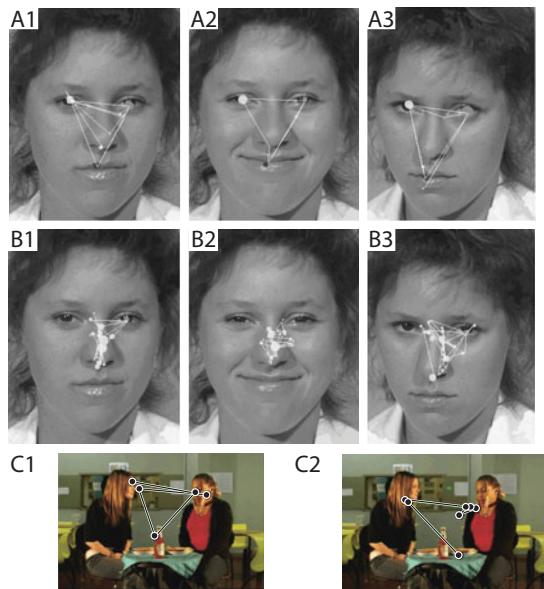


Figure 26-1. Visual scanpaths can be obtained from human subjects by videotaping an eye at high resolution. The resulting scanpaths map both points of fixation (dots) and saccades (lines) between points of fixation. The scanpaths of control (A) and schizophrenic (B) individuals are shown as the subjects look at a neutral face (A₁, B₁), a happy face (A₂, B₂), and a sad or somber face (A₃, B₃). As illustrated by these representative scanpaths, schizophrenic subjects spend far less time fixating on the eyes and mouth, the most emotionally salient features of a human face, than do control subjects. In contrast to control subjects who showed similar scanpaths regardless of the target expression (A₁-A₃), schizophrenic subjects followed more normal scanpaths when looking at a sad face (B₃) than at neutral (B₁) or happy (B₂) faces. Associated with the different scanpaths, schizophrenic subjects judged sad faces as accurately as did controls, but were worse at detecting neutral and happy faces. C: Control teenagers, teenagers with autism spectrum disorder and impaired language development (C₁), and teenagers with autism spectrum disorder and normal language development (C₂) were shown a video of two young women in a restaurant talking about whether to send back disgusting food. Control teenagers (not shown) and teenagers with autism spectrum disorder and language impairment fixated primarily on the eyes of the two faces in the video. In contrast, teenagers with autism spectrum disorder and normal language skills fixated on eyes far less. Further, the amount of time spent fixating the mouth was directly correlated and the amount of time fixating the eyes indirectly correlated to language skills among subjects with autism spectrum disorder.

Panels A and B are modified from Loughland, C.M., Williams, L.M., and Gordon, E. Visual scanpaths to positive and negative facial emotions in an outpatient schizophrenia sample. *Schizophrenia Res* 55: 159-70, 2002, where a full discussion of these interesting results can be found, with permission of the publisher, Elsevier. Panel C is modified from Norbury, C.F., Brock, J., Cragg, L., Einav, S., Griffiths, H., and Nation, K. Eye-movement patterns are associated with communicative competence in autistic spectrum disorders. *J Child Psychol Psychiatry* 50: 834-42, 2009, where these intriguing results are discussed fully, with permission from the publisher, John Wiley & Sons.

- Four types of eye movements serve to change the direction of fixation:
 - *Cancellation* of the vestibuloocular reflex during head movements allows gaze to shift from one location to another.
 - *Saccades* are rapid, 200 or more degrees per second, ballistic movements that move the eyes to a new position in minimum time.
 - In *smooth pursuit*, the eyes move slowly, at about 20–50 degrees per second, to follow a moving target such as a bird flying.
 - *Vergence* is part of the near triad that shifts the fixation target from a far location to a near location.

We start our discussion of the oculomotor system by considering a few peculiar properties of extraocular muscles and motoneurons.

SMALL GAZE SHIFTS DEPEND PRIMARILY ON EYE MOVEMENTS.

The direction of our gaze depends on the position of our head, as well as on the direction of fixation. Recall from Box 19-1 that eye movement contributes more than does head movement to gaze shifts, small and large alike. Moreover, since saccades are faster and start earlier than head movements, they bring gaze to a new position before head movement makes any appreciable contribution (Fig. 26-2). Whereas the gaze shift ends immediately after the saccade finishes, the head continues to move after the saccade is over. At this point, the eyes *retrace* their trajectory to move *back* to the target, and they do so at the slow pace of the head movement. As a consequence, gaze is steady from the point at which the eyes reach the target onward.

Progressive external ophthalmoplegia is a disorder that results in progressive weakness and

eventual failure of all extraocular muscles and the levators palpebrae. Sporadic mutations in any of a number of mitochondrial genes coding for enzymes in the respiratory chain cause progressive external ophthalmoplegia. Initially, weakness is usually bilaterally symmetric and head movements compensate for the loss in extraocular mobility. However, eventually it becomes obvious to the patient, or to those around the patient in pediatric cases, that the eyes are not moving and that head movements are producing all gaze shifts. Over time, facial muscles and the long muscles of the legs become weak. Surgery is typically used to treat the ptosis resulting from levator palpebrae involvement but no therapy currently exists for the ophthalmoplegia.

EXTRAOCULAR MUSCLES AND NEUROMUSCULAR JUNCTIONS HAVE SPECIAL PROPERTIES ADAPTIVE TO THEIR FUNCTION

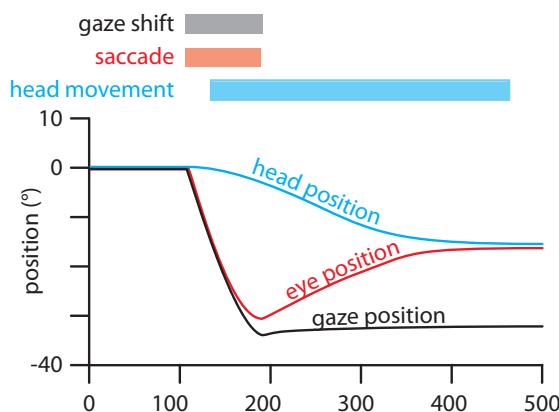


Figure 26-2. During large gaze shifts, both the eyes and head move in the direction of the target. The eyes start moving before the head and bring gaze most of the way to the final target position before the head movement moves by any appreciable amount. After the new gaze position is reached, the head keeps moving as the eyes *retrace* their position. The eyes move away from the target at exactly the same rate that the head moves toward the target. The result is that gaze stays steady once the target has been reached.

Modified from Freedman, E.G. Coordination of the eyes and head during visual orienting. *Exp Brain Res* 190: 369–87, 2008, with permission of the publisher, Springer.

Extraocular muscle fibers are heterogeneous, comprising at least six subtypes, all of which are distinct from the skeletal muscles found in the trunk and limbs. There are two layers of extraocular muscle fibers: (1) **global fibers** that insert on the globe and provide the force to rotate the eye, and (2) **orbital fibers** that insert on the orbit and modify the pulling direction of the global fibers. About a fifth of the global fibers are unusual in several ways that make them ideally suited to keeping the eye in an eccentric position for an extended period. These global muscle fibers are innervated by multiple motoneurons, and they do not fire action potentials. Instead, multiply innervated

Box 26-3

EXTRAOCULAR TISSUE IS SUSCEPTIBLE TO AUTOIMMUNE DISEASE.

Myasthenia gravis and **Grave's ophthalmopathy** are two autoimmune diseases that target ocular tissues. Myasthenia gravis is an autoimmune disease that results in failure of the neuromuscular junction (see Box 8-6). Patients typically present with ptosis and diplopia secondary to extraocular weakness. Note that diplopia results if the two eyes are unyoked by even the minutest amount. Figure 26-3 shows 20° vertical eye movements made by a control subject with normal eye movements and by a patient with mild myasthenia gravis. In the patient, the positions of the two eyes are different from one another by only a degree or two at the most. Yet, this small relative displacement is enough to produce diplopia.

Grave's ophthalmopathy is an inflammation of the orbit typically associated with hyperthyroidism. Antibodies against antigens present in the orbit drive an inflammatory reaction that produces extreme swelling of the orbital contents, including the muscles. Consequences include **proptosis**, or bulging of the eye, that is usually accompanied by pain, restriction of eye movements, and in extreme cases, compression of the optic nerve, resulting in blindness. The vulnerability of the extraocular muscles to these two autoimmune diseases may reflect a unique immunological milieu within the orbit.

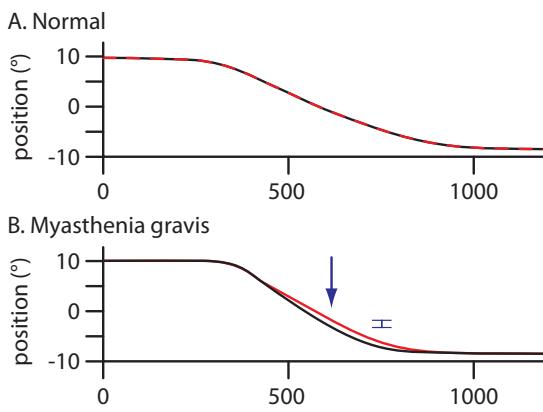
global muscle fibers produce graded contractions that are fatigue-resistant, characteristics ideally suited to sustaining an eccentric eye position. Most global extraocular muscle fibers contract rapidly, resembling fast-twitch muscle fibers in this respect. Yet, they resemble slow-twitch fibers in that they are optimized for oxidative energy consumption. In fact, the metabolic profile of extraocular muscles is similar to that of the muscles used by hummingbirds to fly.

Neuromuscular junctions on extraocular muscles have less area than do neuromuscular junctions found elsewhere. In addition, the acetylcholine receptor at extraocular neuromuscular junctions is the receptor isoform found at limb and trunk muscles during embryonic development. The upshot is that there is a lower safety factor at extraocular neuromuscular junctions. The lower safety factor is in part compensated for by the high, ongoing discharge of extraocular motoneurons. The peak firing rate of extraocular motoneurons is around 600 Hz, in comparison to about 150 Hz for motoneurons innervating limb skeletal muscles. As a result of the high discharge rates of extraocular motoneurons, extraocular muscles are likely to rapidly reach a steady level of contraction rather than to twitch. The steady contraction is akin to a fused tetanus except that further increases in motoneuron discharge rate generate larger forces. By using changes in discharge rate to control muscle tension, extraocular motoneurons produce smooth increases in the forces acting upon the globe. A number of autoimmune diseases target ocular tissues including muscles of the globe and result in slow or weak eye movements (see Box 26-3).

FIXATION AT AN ECCENTRIC POSITION REQUIRES SUSTAINED MUSCULAR FORCE

The tonic discharge rate of extraocular motoneurons depends on eye position. In the neutral position, when the eye is not rotated in the pulling direction of any muscle, extraocular motoneurons have a resting discharge (Fig. 26-4A). As the eye deviates from the neutral position, the tonic firing rate changes in proportion to the distance the eye has been rotated from the neutral position in the pulling direction of the target muscle. The firing rate increases when the eye moves in the pulling direction of the innervated muscle and decreases when the eye moves in the opposing direction. For example, when the eye is abducted all the way to the left, the left lateral rectus and right medial rectus are fully contracted, and the right lateral rectus and left medial rectus muscles are fully relaxed. Motoneurons innervating the fully contracted muscles fire at an elevated rate, whereas those innervating relaxed muscles may pause or fire very infrequently (Fig. 26-4B). If the eye were abducted just 5–10 degrees to the left, the discharge rate of left lateral rectus and right medial rectus motoneurons would increase less than is the case in the fully abducted position (Fig. 26-4C). Similarly, the discharge rate of right lateral rectus and left medial rectus motoneurons would decrease below the discharge rate in the neutral position but would not pause. The superior and inferior recti and the superior and inferior obliques do not change their firing rate during eye abduction or adduction. This is because none of these muscles pull the eye in the medial-lateral direction.

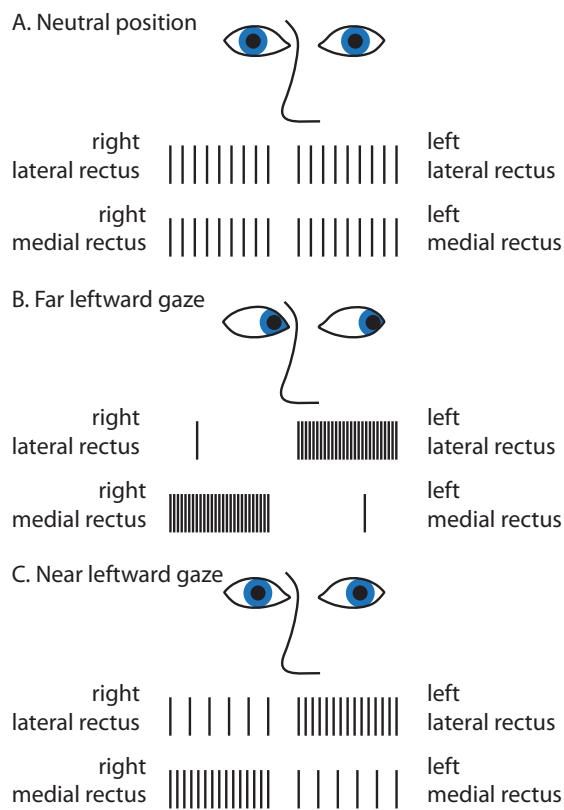
Figure 26-3. Precisely aligned eye movements are necessary for normal vision. A: In healthy individuals with normal eye movements, the vertical positions of the right (red) and left (black) eyes are the same at every moment in time as a person shifts gaze from up to down. Therefore, traces of the two eye positions overlap completely. The traces are alternately dashed in order to illustrate the overlap. In a patient with mild myasthenia gravis, a neuromuscular disease that typically affects eye muscles first, the two eyes are misaligned (arrow). Even a small misalignment of a degree or two produces diplopia. The distance between the eye positions at the time of the arrow is illustrated by the lines to the right. Modified from Kaminski, H.J., Li, Z., Richmonds, C., Ruff, R.L., and Kusner, L. Susceptibility of ocular tissues to autoimmune diseases. *Ann N.Y Acad Sci* 998: 362–74, 2003, with permission of the publisher, John Wiley & Sons.



THE VESTIBULOOCULAR REFLEX ENSURES A STEADY FIXATION TARGET DURING HEAD AND BODY MOVEMENTS

The *vestibuloocular reflex*, or **VOR**, keeps the image on the fovea stable even as the body and head move about. Essentially, this reflex allows us to read as we walk, ride public transit, or sit in a moving train. In fact, since we are never *perfectly* still, the vestibuloocular reflex also permits us to read, or see any image

Figure 26-4. The tonic firing rate of extraocular motoneurons is related to the distance the eye has been rotated from the neutral position in the pulling direction of the target muscle. In the neutral position (A), all extraocular muscles are at rest and all extraocular motoneurons have a resting discharge. During fixation to the far left (B), the left lateral rectus and right medial rectus motoneurons have an elevated discharge rate, whereas the right lateral rectus and left medial rectus motoneurons do not fire or fire very infrequently. During fixation to the near left (C), the left lateral rectus and right medial rectus motoneurons fire at a rate intermediate between the rates during the above two conditions. Similarly, the right lateral rectus and left medial rectus motoneurons fire at a rate below that of resting levels.



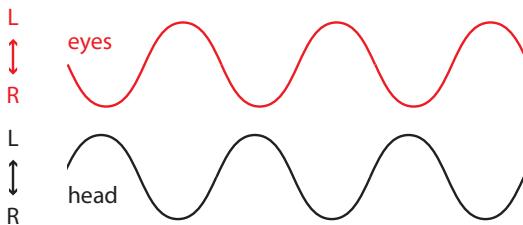


Figure 26-5. The vestibuloocular reflex keeps gaze stable during head movements. When the head (black) rotates back and forth in the yaw plane, the eyes move in the opposing direction due to the vestibuloocular reflex. L: left; R: right.

stably as we stand—sway—or sit. Through the vestibuloocular reflex, every head movement elicits an eye movement in the opposite direction (Fig. 26-5).

To appreciate the advantages accrued by using *vestibular* input rather than *visual* input, do the following experiment. Fixate on your finger in front of your face. Now, turn your head back and forth in the yaw plane. Start slowly and increase the speed of your

head movement until your finger gets blurry. You have to move your head fairly fast in order to blur the image of your finger. Now, keep your head steady and move your finger, at first slowly and then more rapidly. Hopefully, you realize that you are much better at stabilizing gaze during head movements than during movements of the visual target. There are many reasons why this is so, starting with the respective transduction mechanisms. Vestibular transduction depends on mechanoreceptive ionotropic channels, whereas visual transduction depends on metabotropic receptors. In fact, processing of a visual stimulus is still in the retina by the time that a vestibular input has already reached the brainstem. Moreover, in order to use visual input to stabilize gaze, *retinal slip*, meaning movement of an image across the retina, needs to be detected. Processing visual information to detect retinal slip takes time. Just as vestibular input is most effective in stabilizing retinal images, gyroscopes have greatly improved the image quality obtained by cameras with *optical image stabilization*.

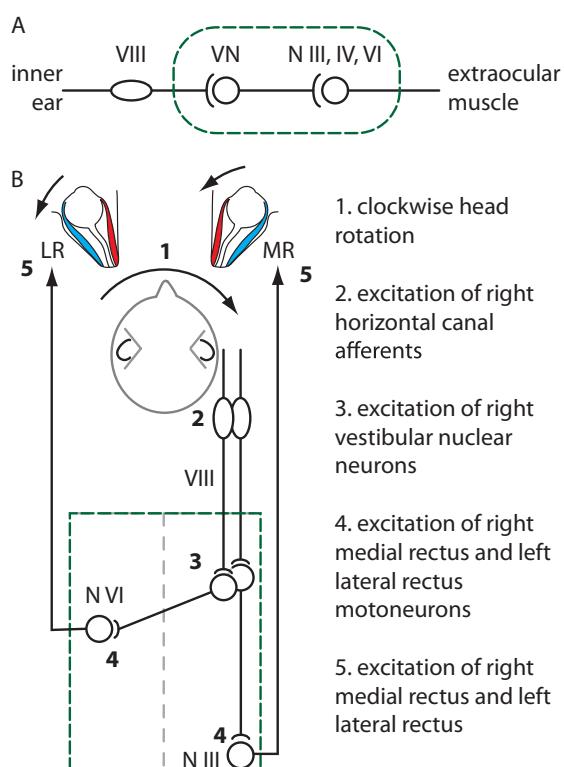
The vestibuloocular reflex is a disynaptic reflex and requires three neuronal types (Fig. 26-6A):

- Primary vestibular afferent
- Vestibular nuclear neuron
- Extraocular motoneuron

We start by considering the simplest case which is, of course, a rotation in the yaw plane (see Chapter 19). Consider a clockwise head rotation that excites afferents innervating the right horizontal semicircular canal. Vestibular afferents from the right horizontal canal excite vestibular nuclear neurons (Fig. 26-6B). Vestibular nuclear neurons in turn directly excite ipsilateral medial rectus motoneurons and contralateral lateral rectus motoneurons. The final result is contraction of the left lateral rectus and right medial rectus. On the left side the circuit is, of course, identical. The difference is that left horizontal semicircular canal afferents are inhibited rather than excited by a clockwise head rotation. This in turn leads to less excitation, or a *disfacilitation*, of left vestibular nuclear neurons. In turn, the discharge of left medial rectus motoneurons and right lateral rectus motoneurons decreases.

Through the disynaptic circuitry of the vestibuloocular reflex, head rotation leads to excitation and inhibition of extraocular motoneurons in a pattern that produces an opposing eye movement. The specificity of the reflex arises from the

Figure 26-6. A: The vestibuloocular reflex is a disynaptic, three-neuron reflex. Vestibular afferents (VIII) enter the central nervous system (dashed green line) and synapse on neurons in the vestibular nuclei (VN). Vestibular nuclear neurons project to extraocular motoneurons in cranial nerve nuclei (N III, IV, VI) and spinal motoneurons that innervate neck muscles (not shown). B: The circuit of a horizontal vestibuloocular reflex evoked by clockwise head rotation (↑) is diagrammed. Clockwise head rotation excites right horizontal canal afferents (VIII, 2), which then excite vestibular nuclear neurons (3). Vestibular nuclear neurons in turn excite contralateral abducens motoneurons and ipsilateral medial rectus motoneurons (4). The result is contraction of the contralateral lateral rectus and ipsilateral medial rectus (5), producing a contralateral, in this case counterclockwise, eye movement. Thus, a head rotation elicits a compensatory eye movement in the opposite direction. Note that left vestibular afferents decrease their discharge rate from resting levels in response to a clockwise head rotation. Through the same circuit as illustrated for the right side, the decrease in left vestibular afferent discharge produces a relaxation in right lateral rectus and left medial rectus.



connectivity of vestibular nuclear neurons. Afferents from each canal pair are connected to a pair of extraocular motoneuron pools, one ipsilateral and one contralateral, by vestibular nuclear neurons (see Table 26-1). In this way, head movement that stimulates a canal pair elicits eye movement in the opposing direction.

By now, the reader is comfortable with the excitation of ipsilateral medial rectus motoneurons and contralateral abducens motoneurons by horizontal canal activation. The other two extraocular muscle pairs are (1) the inferior oblique and contralateral superior rectus, which produce a half-upward and half-lateral eye movement; and (2) the superior oblique and contralateral inferior rectus, which produce a half-downward and half-lateral eye movement. As the reader may have suspected, the half-vertical and half-horizontal eye movements are in the planes of the two posterior-anterior canal pairs. In sum, vestibuloocular circuitry uses synaptic connectivity to automatically link the planar components of a head movement to the motoneurons that will lead to an opposing eye movement. The circuitry requires a minimum of neural processing and therefore is complete within a very short time. In the human, a head movement elicits opposing eye movements in only 10–15 ms!

All head movements, not just rotational ones, elicit compensatory eye movements. The translational vestibuloocular reflex elicits translational eye movements in response to translational head movements. In addition, the **vestibulocollic reflex** produces head movements that oppose head rotations. The vestibulocollic reflex depends on circuitry that closely parallels that of the vestibuloocular reflex except that the targeted motoneurons innervate neck muscles. Second, the latency of the vestibulocollic reflex is a little longer than that of the vestibuloocular reflex. Nonetheless, the vestibulocollic reflex can compensate, at least partially, for the

TABLE 26-1. THERE ARE THREE PLANES AND SIX DIRECTIONS OF ROTATIONAL HEAD MOVEMENT

HEAD MOVEMENT	EXCITED CANAL	INHIBITED CANAL	EXCITED EXTRAOCULAR MUSCLE PAIR	EYE MOVEMENT
Clockwise rotation	Right horizontal canal	Left horizontal canal	Left lateral rectus and right medial rectus	Counterclockwise
Counterclockwise rotation	Left horizontal canal	Right horizontal canal	Right lateral rectus and left medial rectus	Clockwise
Half pitch forward + half roll right	Right anterior canal	Left posterior canal	Left inferior oblique and right superior rectus	Up and to the left
Half pitch backward + half roll left	Left posterior canal	Right anterior canal	Right superior oblique and left inferior rectus	Down and to the right
Half pitch forward + half roll left	Left anterior canal	Right posterior canal	Left inferior oblique and left superior rectus	Up and to the right
Half pitch backward + half roll right	Right posterior canal	Left anterior canal	Left superior oblique and right inferior rectus	Down and to the left

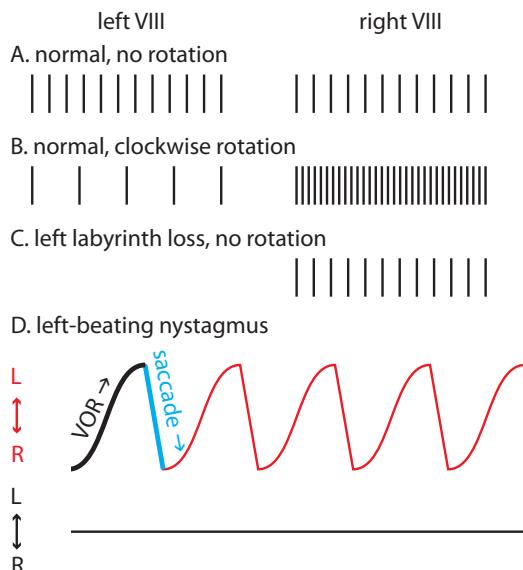
For each direction of head movement, the vestibulocular reflex involves the excitation of a pair of extraocular muscles and an eye movement in the opposing direction.

vestibuloocular reflex in individuals with extraocular muscle or motoneuron impairment.

NYSTAGMUS CAN RESULT FROM UNBALANCED PERIPHERAL VESTIBULAR INPUT

Ordinarily, the paired semicircular canals provide a balanced signal to the left and right vestibular nuclei (Fig. 26-7A). However, some pathological conditions produce an imbalance in the left and right vestibular inputs (Fig. 26-7C). For example, imagine that the left semicircular canals were impaired by a toxic reaction, surgery, trauma, or infection. If one labyrinth is inoperative, there is no activity in vestibular afferents on that side. Yet, the contralateral inner ear functions normally, so that there is normal resting discharge in vestibular afferents on the healthy side. The imbalance in afferent input to the vestibular nuclei (Fig. 26-7C) resembles the imbalance produced by an ipsilateral rotational head movement (Fig. 26-7B). The nervous system therefore interprets the imbalance as an ipsilateral rotational head movement. The result is a vestibuloocular reflex to the contralateral side (VOR in Fig. 26-7D). Once the eye reaches the edge of the orbit, a quick saccade to the ipsilateral side is made (saccade in Fig. 26-7D). At this point, the imbalanced afferent input still exists, and so another compensatory eye movement to the contralateral side is made, setting off another saccade, and so on and on. This repeated

Figure 26-7. A: At rest and in the absence of any head rotation, activity in the left and right horizontal canal afferents is balanced. B: During clockwise head rotation, activity in left horizontal canal afferents is decreased, and activity in right horizontal canal afferents is increased. C: When one labyrinth is injured or surgically removed, there is no more input from the vestibular afferents on that side. The afferents contralateral to the damage continue to fire, leading to an imbalance in the vestibular input from the two sides. Thus, in a person with unilateral vestibular damage, the vestibular input resembles the input arising during head rotation, even when the individual is at rest and the head is not rotating. D: Unilateral vestibular damage leads to a nystagmus that beats away from the direction of the damage. This nystagmus consists of a vestibuloocular reflex (VOR) toward the side of the damage followed by a fast reset (saccade) in the direction away from the side of the damage. Note that the nystagmus occurs in the absence of any head rotation (flat black line).



cycle of a slow eye movement in one direction followed by a fast reset in the opposite direction is termed **jerk nystagmus** (Fig. 26-7D).

The **fast phase** of jerk nystagmus is always a saccade. In the case of nystagmus of peripheral origin, the **slow phase** of the nystagmus is a vestibuloocular reflex. The pathology involved in nystagmus is the eye movement during the slow phase. However, the saccade is what stands out when observing nystagmus in real time. Therefore, the direction of a nystagmus is named for the direction of the saccade involved.

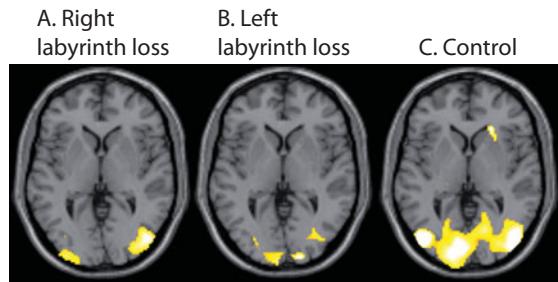


Figure 26-8. Patients with unilateral vestibular loss learn to suppress visual motion. Functional magnetic resonance images from patients with failure of the right (A) or left (B) vestibular apparatus and from controls (C) were obtained during optokinetic nystagmus, a physiological form of nystagmus that can be elicited by a repeating visual pattern (see text). The scans are horizontal sections with the occipital cortex at the bottom. Patients showed less activation of visual areas of cortex than did control patients. This was interpreted as evidence that the patients were effectively suppressing visual motion stimulation and thus had smaller responses to the oscillopsia accompanying optokinetic nystagmus. Reprinted from Deutschlander A., et al. Unilateral vestibular failure suppresses cortical visual motion processing. *Brain* 131: 1025-34, 2008, with permission of the publisher, Oxford University Press.

Consider what happens to the visual scene during nystagmus. As one or both eyes oscillate back and forth, so does the visual scene. This can produce **oscillopsia**, meaning that the visual image moves even when the head is stationary and no *intentional* eye movements are taking place. Note that when both eyes move together, oscillopsia occurs *without diplopia*. Luckily, the perception of oscillopsia can be suppressed. Individuals born with a form of congenital nystagmus, including patients with albinism or Down syndrome, suppress visual motion and therefore rarely report oscillopsia. In fact, if the retinal image of individuals with congenital nystagmus is stabilized, the patients then report oscillopsia. This indicates that patients learned at an early age to effectively suppress visual motion all the time. Suppression continues when the visual image is artificially stabilized, so that the suppression then is perceived as visual motion! Adults who acquire a form of nystagmus learn to suppress visual motion and thus eventually largely ameliorate the perceptual effects of nystagmus (Fig. 26-8).

Nystagmus comes in many different forms and can result from either peripheral or central lesions (see Box 26-4). Nystagmus resulting from a peripheral lesion is the easiest to understand mechanistically. Caloric testing is a noninvasive clinical method which can be

Box 26-4

THERE ARE MANY TYPES OF NYSTAGMUS ARISING FROM A VARIETY OF LESION SITES.

Nystagmus occurs after peripheral or central lesions in a number of locations. Determining the underlying cause of nystagmus is definitely a task for a specialist. Nonetheless there are a few key differences between nystagmus that arises from a peripheral lesion and that which arises from a central lesion (Table 26-2).

Several types of nystagmus are named for the direction of movement involved. For example, a *downbeat nystagmus* has a slow upward phase followed by a fast downward resetting saccade. *Torsional nystagmus*, almost always due to a central

lesion, involves a slow torsional movement in one direction, either intorsion or extorsion, followed by a fast torsional movement in the opposite direction.

Nystagmus that involves a slow and a fast phase, termed *jerk nystagmus*, is most common. However, a different form of nystagmus, termed **pendular nystagmus**, involves the eyes moving back and forth like a pendulum. In other words, in pendular nystagmus, the eyes oscillate back and forth in a pattern that resembles the eye movements used to watch a tennis volley. Pendular nystagmus often occurs in individuals suffering from multiple sclerosis.

used to diagnose peripheral vestibular lesions (see Box 26-5). Nystagmus can also result from central lesions to a number of structures including the vestibular nuclei, horizontal and vertical gaze centers, and the cerebellum even in individuals with a healthy peripheral vestibular system.

THE VESTIBULOOCULAR REFLEX IS CONSTANTLY MODULATED BY THE CEREBELLAR FLOCCULUS

We change the gain in the vestibuloocular reflex all the time, and of course we do this without any conscious involvement. A few examples will illustrate the incredible flexibility of the vestibuloocular reflex. Sometimes the vestibuloocular reflex is *turned off*, meaning the gain is set to zero. *Cancellation of the vestibuloocular reflex* occurs during voluntary shifts in gaze.

TABLE 26-2. PERIPHERAL AND CENTRAL LESIONS CAN BOTH LEAD TO NYSTAGMUS. HOWEVER, THE CHARACTERISTICS OF THE NYSTAGMUS IN THE TWO CASES ARE OFTEN DIFFERENT.

PERIPHERAL LESION	CENTRAL LESION
Unidirectional	Uni- or bidirectional
Typically horizontal; rarely torsional	May be horizontal, vertical, or torsional
Tinnitus or hearing loss often present as well	Tinnitus or hearing loss not present
Usually associated with a sense of vertigo	May occur without vertigo

Box 26-5

CALORIC TESTING IS A WAY TO TEST FOR PERIPHERAL VESTIBULAR HEALTH BY INTENTIONALLY ELICITING NYSTAGMUS.

Caloric testing uses hot and cold water to artificially evoke nystagmus to test peripheral vestibular function. A person is laid in a supine position, which places the horizontal canal in the vertical plane. Recall that the hair cells in the ampullae of the horizontal semicircular canals are at the anterior end of the canals and are oriented toward the utriculus. In a supine individual, then, the hair cells are at the upper end of the horizontal canal and, importantly, are above the level of the external auditory meatus. Warm or cold water is then introduced into the external auditory meatus. When warm water is placed in the ear, endolymph flows up—as warm water rises—which results in excitation of the hair cells in the horizontal canal ampulla. Although the head has not moved, the brain receives a signal that the head is rotating toward the ipsilateral side. This evokes a vestibuloocular reflex toward the contralateral side. The eye comes to the end of the orbit and

quickly resets to the ipsilateral side. Still receiving the message that the head is rotating toward the ipsilateral side, another vestibuloocular reflex toward the contralateral side occurs and so on. In this way, warm water evokes an ipsilateral-beating nystagmus (remember that nystagmus is named for the direction of the quick reset). By similar reasoning, please convince yourself that cold water elicits a nystagmus to the opposite side. Thus, the best mnemonic in neurobiology is born: COWS—cold opposite, warm same—referring to the direction of the nystagmus (not the direction of the vestibuloocular reflex) elicited by irrigating cold or warm water into the ear. Caloric testing is often used to test vestibular and oculomotor system function in comatose or minimally responsive patients. As these patients will not follow instructions to follow a target, caloric testing is the only way to determine if their vestibuloocular pathways are intact.

The inability to turn off the vestibuloocular reflex is termed **doll's eyes** and is a common sign of coma (see Box 26-6).

The gain of the vestibuloocular reflex also changes when switching between near and far viewing. This is easy to visualize. Simply ask a friend to fixate on a near target, a finger, or on a far target, a tree at the horizon, and move her head back and

Box 26-6

DOLL'S EYES ARE A SIGN OF A COMATOSE PATIENT WITH INTACT VESTIBULOOCULAR PATHWAYS.

A neurologically normal awake person can cancel the vestibuloocular reflex as occurs all the time during voluntary gaze shifts. However, a comatose or minimally responsive individual never cancels the vestibuloocular reflex. For example, consider a person lying supine in bed—doll's eyes usually occur in a recumbent individual—and looking up. If a physician turns this individual's head to the right or the left, the eyes continue to look straight up. Thus, a person with

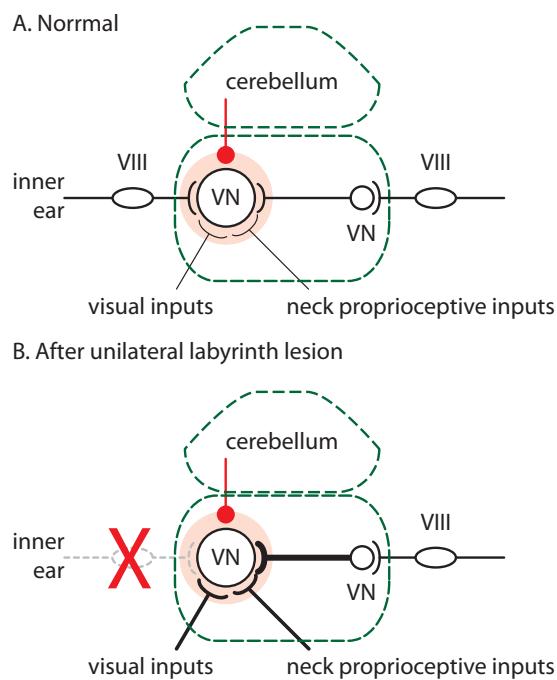
doll's eyes keeps their eyes fixated straight ahead regardless of the position of the head. This behavior renders an appearance very similar to the look of the eyes in a doll, giving rise to the term. The only thing worse than doll's eyes is the absence of a vestibuloocular reflex altogether. If the eyes move together when the head is rotated and caloric testing evokes no response, the vestibuloocular pathways are damaged, suggesting widespread brainstem damage.

forth in the yaw plane. You will see that your friend's eyes move far more when viewing a near than a far target. The gain of the vestibuloocular reflex is greater during near viewing than far viewing. The reason that we are able to effectively fixate near and far targets during head movements is because the cerebellum seamlessly modulates the gain of the vestibuloocular reflex. The flocculus also adjusts the gain and timing of the vestibuloocular reflex to changing conditions, such as occur when adapting to a new pair of glasses or after damage to the inner ear.

The cerebellar flocculus adjusts the gain of the vestibuloocular reflex by modulating the synapse between vestibular afferents and vestibular nucleus neurons (Fig. 26-9A). Purkinje cells in the flocculus receive information about eye and head movements through parallel fibers and visual information through climbing fibers. When retinal slip is detected, output from the flocculus adjusts the vestibular nuclear synapse to minimize retinal slip during ensuing head movements. In this way, the flocculus mediates short-term motor learning. An individual with floccular damage cannot change the vestibuloocular reflex gain.

The flocculus can also induce long-term changes in the synaptic weights of a variety of inputs to vestibular nuclear neurons. After injury to a vestibular end organ, the flocculus can modify the weight given to incoming signals from the contralateral ear, from neck proprioceptors and from visual pathways (Fig. 26-9). In essence, the flocculus can turn off the influence of afferents from the injured ear and increase the weight given to inputs from other sources. Often, visual input comes to dominate the vestibuloocular reflex after vestibular injury. In such cases, the vestibuloocular reflex is performed well as long as the lights are on but not in the dark. In sum, the vestibuloocular reflex can be modified to function after many types of injury. However, after floccular damage, the vestibuloocular reflex becomes immutable and therefore its usefulness is severely compromised.

Figure 26-9. The cerebellum, principally the posterior vermis, uvula, nodulus, and flocculus modulate the synapses onto vestibular nuclear neurons (VN). In a healthy individual with the eyes open, the predominant inputs to the vestibular nucleus arise from the vestibular nerve (VIII). Ipsilateral vestibular afferents synapse directly on vestibular nuclear neurons, whereas commissural pathways bring input from the contralateral vestibular apparatus. There are also visual and neck proprioceptive inputs to vestibular nuclear neurons. By modulating the synapses onto vestibular nuclear neurons, as well as the neurons themselves, the cerebellum can change the gain of the vestibuloocular reflex as conditions warrant. The light red area encircles the neural elements that are most heavily influenced by cerebellar output. Cerebellar Purkinje cells in the flocculus project directly into the vestibular nuclei. In this way, the vestibular nuclei are analogous to deep cerebellar nuclei. **B:** After unilateral labyrinth loss (red X), the cerebellum, principally the flocculus, modifies the synaptic strength of inputs to vestibular nuclear neurons. As a result, synaptic inputs from the contralateral ear, as well as from the visual system, are strengthened. Consequently, individuals rapidly compensate for the damaged ear and have a normal or near normal vestibuloocular reflex after a short period of learning. Since visual inputs are far more important after vestibular damage, the vestibuloocular reflex functions far better in the light than in the dark in affected individuals.



OPTOKINETIC RESPONSES GIVE RISE TO PHYSIOLOGICAL NYSTAGMUS

As mentioned in Chapter 19, vestibular hair cells do not respond to head movements that are at a constant velocity or to very slow head movements. As constant velocity and very slow head movements do not engage the vestibular system, the vestibuloocular reflex does not occur in response to either of these stimuli. Yet, we are able to stabilize an image during both constant velocity and very slow head movements. We do this using the *optokinetic response*. In the optokinetic response, movement of the visual field elicits an eye movement in the opposite direction, so that the image on the retina stays steady.

Whole-field visual movement occurs with either self-motion or visual field motion. Examples of the former include looking out of a moving train or rotating around and around on a swivel chair. Visual field motion can be accomplished by passing a repeating visual pattern in front of a stationary individual. Physicians often use a rotating black-and-white striped drum to elicit an optokinetic response. The eyes track the image until the eyes are at the edges of the orbits at which point a quick saccade in the opposite direction is made. This slow eye movement in one direction and fast reset in the other direction constitutes *optokinetic nystagmus*. This form of nystagmus is entirely normal and is in fact a sign of health.

SACCADES ARE BALLISTIC MOVEMENTS THAT ACHIEVE VERY HIGH MOVEMENT VELOCITIES

Saccadic eye movements are ballistic eye movements that change the direction of gaze in order to place a new visual target on the fovea. Saccades can be voluntarily initiated by areas in cortex or can occur more automatically as happens with orienting saccades to an unexpected sound or sight. After the saccade is initiated, its direction and magnitude cannot be changed by changes in target position. Thus, saccades are ballistic (see Chapter 20). The eyes move very quickly during saccades, with eye speeds of up to 600 degrees per second. The saccade itself takes about 200–250 ms to initiate and 50–100 ms to complete (Fig. 26-10A). The size or amplitude of the saccade is the distance, in degrees, between the starting and ending positions. As saccade size increases, the duration and peak velocity of the saccade increase as well.

A saccadic eye movement has two components: **pulse** and **step**. The pulse is the ballistic movement, and the step is the maintenance of the eye in the new desired position (Fig. 26-10A). Although images move across the retina during the pulse portion of a saccade, visual processing suppresses input during the pulse, so that no blur is perceived as the eye moves.

Like the vestibular system, the oculomotor system is a vector-based system. This means that every eye movement is decomposed into its horizontal and vertical components, which are then processed separately by the horizontal and vertical gaze

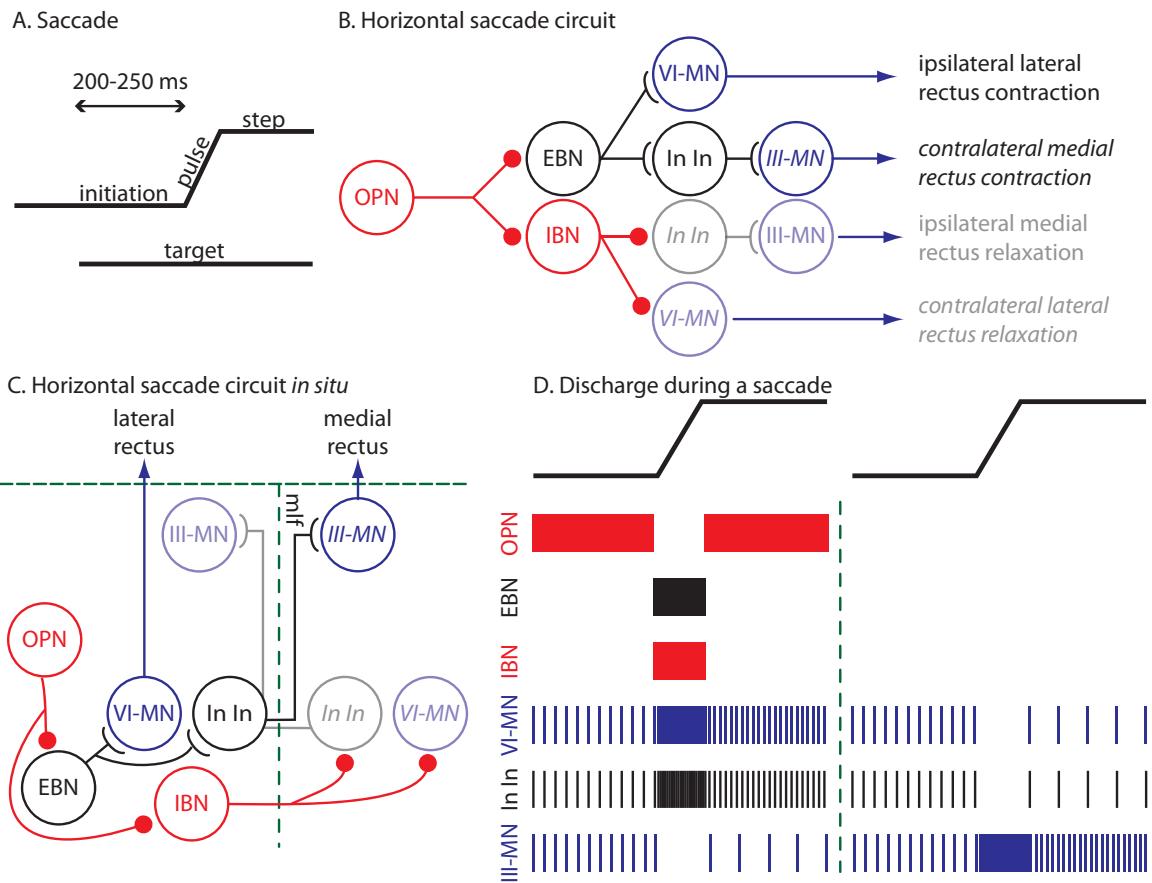


Figure 26-10. Saccades are ballistic movements produced by a circuit consisting of several types of premotor neurons. **A:** A saccade requires 200–250 ms to initiate after a target appears. The actual movement, or pulse, takes 50–100 ms to complete, depending on the distance between the starting position and the target position. **B–D:** The horizontal saccade circuit is illustrated in three different ways. Panel **B** shows a diagram of the connections. In **C**, the same circuit is illustrated within a cartoon of the brain. The view here is looking down on the brainstem with rostral located at the top. In **D**, the firing pattern of each neuron in the circuit is illustrated. Inhibitory omnipause neurons (OPN) suppress (inhibitory neurons are shown in red and inhibitory synapses are symbolized by a filled circle) all activity in excitatory (EBN) and inhibitory (IBN) burst neurons. When the discharge of the omnipause neurons pauses, the excitatory and inhibitory burst neurons burst. Excitatory burst neurons excite ipsilateral abducens motoneurons (VI-MN) and internuclear interneurons (In In). Excitation of the abducens motoneurons leads to contraction of the ipsilateral lateral rectus muscle. Excitation of the internuclear interneurons leads to excitation of the contralateral (*italics*) medial rectus motoneurons (*III-MN*), which in turn produces contraction of the contralateral medial rectus muscle. The burst in inhibitory burst neurons inhibits contralateral abducens motoneurons (VI-MN) and internuclear interneurons (In In), resulting ultimately in the relaxation of the contralateral lateral rectus and ipsilateral medial rectus muscles. In **D**, the effect on neurons of activation of the horizontal gaze center is shown. Traces to the left and right of the green dashed line denote the activity of neurons ipsilateral and contralateral, respectively, to the omnipause neuron. The saccade produced by the activity depicted is reproduced on each side to illustrate the timing of the changes in firing. In sum, a pause in an omnipause neuron evokes a saccade toward that side, termed an ipsilateral saccade.

centers, respectively. The horizontal gaze center is located in the *pontine paramedian reticular formation* (see Chapter 12) surrounding the abducens nucleus. The vertical gaze center is located in the midbrain just rostral and lateral to the oculomotor complex. Thus, there are two brainstem saccade generators—one for the horizontal component and one for the vertical component of every saccade. The neurons that provide the input to these two regions, including the superior colliculus and frontal eye fields, calculate the horizontal and vertical components of a saccade. Information about the horizontal component of an intended saccade is sent to the horizontal gaze center, and similarly, information about the vertical component of an intended saccade

is sent to the vertical gaze center. Horizontal and vertical components of a saccade are then added together again at the level of the muscles.

The next two sections describe the circuits that produce horizontal saccades, which are gaze shifts to the left or right. Analogous circuits control vertical and torsional saccades, but these are not described.

THE CIRCUIT FOR HORIZONTAL SACCADES INVOLVES PREMOTOR NEURONS IN THE HORIZONTAL GAZE CENTER

Saccades are controlled by multiple levels of premotor neurons (Fig. 26-10B–C). The first neurons in the horizontal gaze center to foretell an imminent saccade are **omnipause neurons**. Omnipause neurons fire tonically and then stop firing just before the pulse portion of a saccade. Omnipause neurons are GABAergic and therefore are inhibitory. When they pause, the target neurons, **saccade burst neurons** that are also located in the horizontal gaze center, are disinhibited and fire a burst of activity (Fig. 26-10D). Between saccades, omnipause neurons fire continuously, and burst neurons are silent because they are being inhibited by the omnipause neurons. In order for a saccade to occur, the inhibition of saccade burst neurons must be briefly interrupted, allowing the burst neurons to fire a burst.

There are two types of burst neurons: excitatory and inhibitory. **Excitatory burst neurons** excite motoneurons in the ipsilateral abducens nucleus and **inhibitory burst neurons** inhibit motoneurons in the *contralateral* abducens nucleus. In response to a burst in an excitatory burst neuron, ipsilateral abducens motoneurons fire a burst of action potentials, which pulls the eye laterally. The duration and peak discharge of the burst determine the duration and velocity, and therefore the size, of the saccade. In response to a burst in an inhibitory burst neuron, contralateral abducens motoneurons slow their firing, allowing the eye to be pulled medially.

For horizontal saccades, the two eyes always move together. To accomplish this yoking, there is a special neuron type called the **internuclear interneuron**, which is located in the abducens nucleus. Internuclear interneurons receive the same input as do their neighbors, abducens motoneurons. However, internuclear interneurons do not project to muscle. Instead, they carry a copy of the message received by abducens motoneurons to contralateral medial rectus motoneurons. This pathway serves to yoke the contralateral medial rectus muscle to the lateral rectus muscle, so that the two eyes move together in the horizontal plane. The axons of internuclear neurons cross the midline at the level of the abducens nucleus, and course rostrally in the contralateral medial longitudinal fasciculus to the oculomotor nucleus. Medial longitudinal fasciculus axons are heavily myelinated, which allows for rapid conduction between the abducens and oculomotor nuclei. The heavy myelination also makes medial longitudinal fasciculus axons vulnerable to demyelinating diseases, such as multiple sclerosis. A common symptom of multiple sclerosis, which causes central demyelination, is **internuclear ophthalmoplegia**, in which the eye ipsilateral to the demyelination does not adduct during gaze to the contralateral side (see Box 26-7).

It should be noted that for the two extraocular muscle pairs involved in vertical gaze, one muscle in each pair is innervated by contralaterally located motoneurons. The trochlear nerve crosses the dorsal midline to innervate the contralateral superior oblique (see Chapter 10). Motoneurons in the oculomotor nucleus that innervate the superior rectus send their axons across the midline before exiting the brainstem. Thus, motoneurons innervating each of the muscles in the superior rectus-inferior oblique and inferior rectus-superior oblique pairs are located on the same side. This arrangement facilitates yoking of paired muscles much as do the internuclear interneurons.

It is important to remember that the horizontal gaze center serves horizontal saccades and the horizontal component of smooth pursuit movements. The horizontal gaze center does *not* participate in vergence, even though vergence involves the medial rectus muscles. *Vergence is controlled by neurons in the midbrain.* Therefore, damage

Box 26-7

INTERNUCLEAR OPHTHALMOPLEGIA DISCONNECTS MEDIAL RECTUS MOTONEURONS FROM THE CONTRALATERAL ABDUCENS NUCLEUS.

The message that arises from saccadic burst neurons to abducens motoneurons is copied to medial rectus motoneurons by a special class of neurons in the abducens nucleus, the internuclear interneurons. Internuclear interneurons are not motoneurons. Instead, they project within the central nervous system, connecting the abducens nucleus to the medial rectus motoneuron pool in the contralateral oculomotor nucleus.

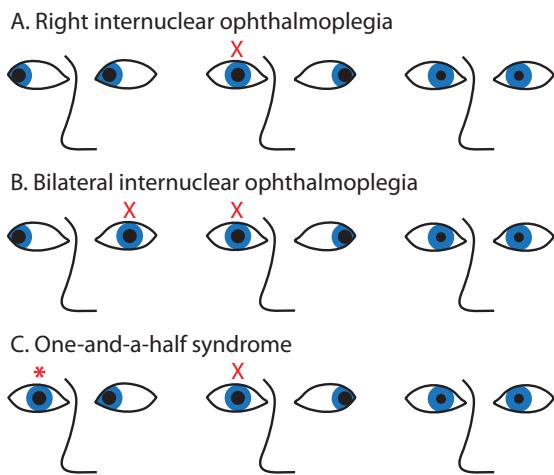
Internuclear interneuron axons follow a stereotyped trajectory from the abducens nucleus to the contralateral oculomotor nucleus. These axons cross the midline at the level of the abducens nucleus and then travel rostrally in the medial longitudinal fasciculus to reach the oculomotor nucleus. Unilateral lesions in the medial longitudinal fasciculus, which are not uncommon, produce *internuclear ophthalmoplegia*. The primary symptom produced by internuclear ophthalmoplegia is the failure of the ipsilateral eye to adduct during a contralateral saccade. For example, a person with right internuclear ophthalmoplegia would be able to saccade to the right normally. However, when looking to the left, the left eye would abduct, but the right eye would stay in the neutral position (Fig. 26-11A). Bilateral lesions of the medial longitudinal fasciculus result in the inability to adduct either eye during lateral gaze to either side (Fig. 26-11B). The perceptual

result of this misalignment of the eyes is diplopia, as the images hitting the two retinas are different.

Internuclear interneurons only receive inputs related to saccades. Inputs related to the vestibuloocular reflex reach abducens motoneurons but not internuclear interneurons. Vergence movements involve the medial rectus and do not require lateral rectus contraction. For this reason, internuclear ophthalmoplegia impairs adduction accompanying saccades and smooth pursuit, a related eye movement. However, the vestibuloocular reflex and vergence movements are normal in individuals with internuclear ophthalmoplegia.

The most common causes of internuclear ophthalmoplegia are demyelination due to multiple sclerosis and small ischemic strokes in the dorsal pons. In the latter case, the abducens nucleus may be affected along with the adjacent medial longitudinal fasciculus. When both abducens nucleus and the medial longitudinal fasciculus are lesioned, **one-and-a-half syndrome** occurs (Fig. 26-11C). Individuals with one-and-a-half syndrome cannot abduct the eye ipsilateral to the lesion, a symptom that stems from damage directly to the abducens motoneurons within the abducens nucleus. In addition, these individuals cannot adduct the eye ipsilateral to the lesion during a contralateral saccade. As vergence depends on the medial rectus only, vergence movements remain normal.

Figure 26-11. Internuclear ophthalmoplegia results from damage to the axons of internuclear interneurons as they travel in the medial longitudinal fasciculus. **A:** An individual with right internuclear ophthalmoplegia will be able to look to the right normally (*left column*) but will not abduct the right eye (*red X*) when looking to the left (*middle column*). Vergence (*right column*) is not affected. **B:** An individual with bilateral internuclear ophthalmoplegia cannot adduct either eye (*red X*) when looking to either side (*left and middle columns*). Vergence in this individual is normal (*right column*). **C:** In one-and-a-half syndrome, the medial longitudinal fasciculus and abducens nucleus, on the same side, are damaged, usually by small strokes. Because of damage to the abducens nucleus, the ipsilateral (in this case right) eye cannot abduct (*red asterisk*) during ipsilateral saccades (*left column*). The damage to the medial longitudinal fasciculus prevents the ipsilateral eye from adducting (*red X*) during contralateral saccades (*middle column*). Vergence movements depend on midbrain circuits and not upon connections between the pons and midbrain. Therefore, vergence movements (*right column*) are normal in individuals with a one-and-a-half syndrome as they are in all of the conditions illustrated.



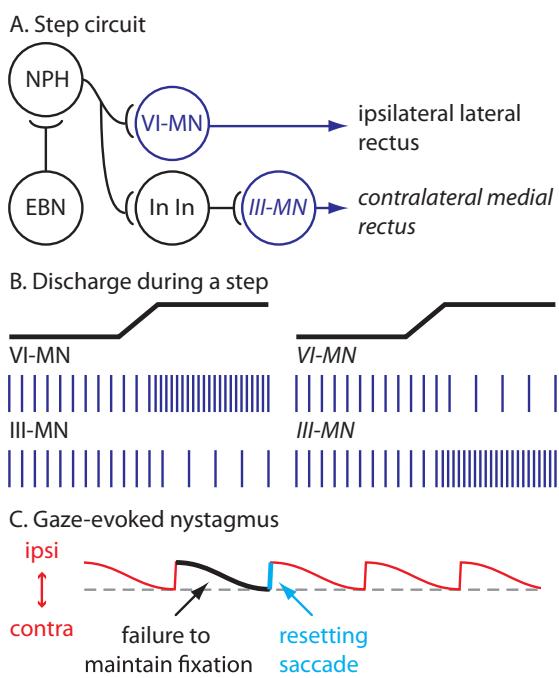
to the internuclear interneurons or even to the abducens nucleus does not impair vergence eye movements. Moreover, vestibular nuclear neurons that mediate the vestibuloocular reflex reach the oculomotor nucleus through a pathway separate from the medial longitudinal fasciculus. Therefore, the vestibuloocular reflex is normal in individuals with internuclear ophthalmoplegia. Of course, damage to the abducens nucleus will prevent all lateral movements of the ipsilateral eye, even those that occur during the vestibuloocular reflex.

The step component of a saccade produces fixation at a new eye position. As mentioned above, fixation is maintained by discharge in extraocular motoneurons that is proportional to the component of eye position in the pulling direction of the innervated muscle. The source of the signal for fixation is the **nucleus prepositus hypoglossi**, which serves as the eye movement integrator for horizontal eye position. Neurons in nucleus prepositus hypoglossi receive input from saccadic burst neurons (Fig. 26-12A) and fire in relation to horizontal eye position. The activity of neurons in nucleus prepositus hypoglossi drives the tonic firing rate of abducens motoneurons, which is needed to maintain an eccentric eye position (Fig. 26-12B). Via the internuclear interneuron, prepositus hypoglossi neurons also excite contralateral medial rectus motoneurons. An impairment of circuits responsible for fixation produces gaze-evoked nystagmus, the most common form of nystagmus (see Box 26-8).

SPECIFIC REGIONS IN THE MIDBRAIN AND CEREBRAL CORTEX INITIATE SACCADES

Activity in several regions can lead to the initiation of saccades. An important presaccadic signal arises from the *superior colliculus*, which contributes to both reflexive orienting saccades and voluntary saccades. The superior

Figure 26-12. At the end of the pulse phase of a saccade, fixation is maintained by discharge in extraocular motoneurons that is proportional to the component of eye position that is in the pulling direction of the innervated muscle. **A:** The circuitry that gives rise to the step component of a horizontal saccade is diagrammed. Nucleus prepositus hypoglossi neurons (*NPH*) receive and integrate input from burst neurons (*EBN*) that produce the pulse component of a saccade. The pulse activity in burst neurons relates to the velocity of the saccade. Thus, integration of this information results in a signal that codes for eye position. Nucleus prepositus hypoglossi neurons send information about eye position to ipsilateral abducens neurons, both motoneurons (*VI-MN*) and internuclear interneurons (*In In*). **B:** As a result, ipsilateral abducens motoneurons and contralateral (*italic*) medial rectus motoneurons (*III-MN*) increase their tonic discharge, whereas contralateral abducens motoneurons (*VI-MN*) and ipsilateral medial rectus motoneurons (*III-MN*) decrease their tonic discharge. **C:** The most common form of nystagmus stems from a failure of the step phase of a saccade. In gaze-evoked nystagmus, the tonic discharge required to maintain an eccentric eye position fails. As a result, the eye relaxes back to the neutral position. The saccade is made again as there is nothing wrong with the pulse component of the saccade. Once again, the eye cannot be maintained at an eccentric eye position, and an oscillatory eye movement occurs. The case illustrated is termed ipsilateral-beating since nystagmus is always named for the direction of the saccade.



Box 26-8

GAZE-EVOKED NYSTAGMUS IS THE MOST COMMON FORM OF NYSTAGMUS.

The most common form of nystagmus is **gaze-evoked nystagmus**, which occurs during fixation at an eccentric position. In gaze-evoked nystagmus, visual fixation cannot be maintained (see Fig. 26-12C). Therefore, the eye relaxes back to the neutral position. There is then a saccade back to the desired point of fixation followed by relaxation back to the neutral position, and so on. Lesions in a number of locations can produce gaze-evoked nystagmus. For example, individuals with a weakness in the abducens nerve may be able to make a saccade to a lateral position but cannot maintain a lateral eye position. This would result in a gaze-evoked nystagmus upon trying to maintain a lateral fixation point.

Another lesion that gives rise to a gaze-evoked nystagmus is a lesion in either of the eye movement

integrators. Eye movement integrators receive information about *all* eye movements and integrate that information to achieve a signal that codes for eye position. There are two such integrators, the nucleus prepositus hypoglossi for horizontal position and the **interstitial nucleus of Cajal** for vertical and torsional eye position. The nucleus prepositus hypoglossi is located in the dorsal medullary midline, just anterior to the hypoglossal nucleus, and the interstitial nucleus of Cajal is located just rostral to the oculomotor complex. Neurons in these nuclei provide continuously updated information about eye position to the vestibular nuclei, cerebellum, and gaze centers. Eye position information is critical to maintaining eccentric fixation and lesions in either integrator result in gaze-evoked nystagmus.

colliculus is organized as a *motor map*, meaning that activity in collicular neurons in any one area produces a gaze shift to a particular location, regardless of the current eye or head position. The superior colliculus selects a target but does not dictate a motor strategy to reach that target. For example, the superior colliculus fires regardless of whether the eyes alone or the eyes and the head are used to shift gaze to a given target. Axons leaving the superior colliculus cross the midline (see Chapter 23). Thus, the superior colliculus projects to the contralateral horizontal gaze center to generate saccades that move the eyes toward the contralateral side.

The superior colliculus can initiate reflexive or automatic orienting movements that occur in response to sensory input signaling an unexpected sound or flash of light. The participation of the superior colliculus in voluntary saccades stems from input that the colliculus receives from a number of cortical regions. The *frontal eye fields* are particularly important as a source of the motor command for volitional saccades. The frontal eye fields contact the contralateral brainstem gaze centers directly and also indirectly via the ipsilateral superior colliculus. A lesion in any of the gaze-control areas of cortex results in impairment of *voluntary* contralateral gaze shifts. In such instances, other eye movements, including the vestibuloocular reflex, vergence, and reflexive orienting gaze shifts remain intact.

SMOOTH PURSUIT CIRCUITS STABILIZE A SLOWLY MOVING TARGET ON THE FOVEA

Smooth pursuit movements are voluntary eye movements that shift the direction of gaze to match a moving target. The velocity of pursuit movements is quite a bit slower than that of saccades. Pursuit movements typically achieve velocities of 50 degrees per second or less and do not exceed 100 degrees per second, far lower than the 300 degrees per second that characterizes most saccades. During pursuit movements, visual perception is maintained. Intriguingly, smooth pursuit movements cannot be “imitated” in the absence of a moving target. In other words, we cannot pretend we are watching a bird fly across the sky. When we try to do this, we make a series of small saccades. Pursuit movements *require* the presence of a slowly moving target and when such a target is present, the velocity of the pursuit movement matches the velocity of the target.

Smooth pursuit movements are initiated by cortical neurons in several regions including the frontal eye fields, the *lateral intraparietal area*, and regions in the dorsal visual stream. Smooth pursuit movements require the contribution of the cerebellar vermis. The cerebellum is thought to adjust smooth pursuit movements so that eye velocity matches target velocity. The same brainstem gaze centers that support saccades also contribute to smooth pursuit. However, the firing patterns of omnipause and burst neurons during smooth pursuit movements are less dramatic. For example, omnipause neurons stop firing altogether during saccades, whereas they decrease their discharge rate without actually pausing during smooth pursuit.

OCULOMOTOR PATHWAYS ARE MODULATED BY BOTH THE CEREBELLUM AND THE BASAL GANGLIA

The oculomotor system, like all other motor systems, is modulated by the cerebellum and basal ganglia, the two great loops of the brain. As is true for other movements, the cerebellum compares actual eye movements to intended eye movements. When movements are off target, the cerebellum provides the fine adjustment needed, so that subsequent eye movements are corrected. The portions of cerebellum most concerned with eye movements are the flocculus, posterior vermis, the nodulus, and the uvula. The uvula and nodulus are most important to gain modulation of the vestibuloocular reflex. The flocculus coordinates eye movements with visual feedback and thus plays critical roles in the adjustment of the vestibuloocular reflex to changing circumstances, to eccentric fixation, and to smooth pursuit movements. The posterior vermis coordinates saccades and smooth pursuit movements. Lesions of the posterior vermis result in dysmetric saccades.

The oculomotor loop of the basal ganglia runs through the caudate and the substantia nigra pars reticulata. As described in Chapter 25, the basal ganglia act like a big wet blanket upon movement. In the case of eye movement, neurons in the substantia nigra pars reticulata have high resting discharge and project to the superior colliculus to inhibit eye movements and other orienting movements. Nigral cells *must pause* in their discharge in order for saccades to occur. In parkinsonian patients, nigral neurons are hyperactive and saccades are slow. In contrast, in patients with hyperkinetic disorders, nigral neurons are hypoactive, resulting in excess saccades and an inability to maintain an eccentric gaze.



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SECTION 6: HOMEOSTASIS

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CHAPTER 27

HOMEOSTATIC SYSTEMS: STAYING ALIVE

Homeostasis is a concept attributed to Walter Cannon, an influential American physiologist of the early 20th century, who coined the term *homeostasis* as well as the phrase *fight-or-flight*. Cannon wrote a book titled *The Wisdom of the Body*, which popularized the idea that the body contains an organized system of defenses that maintain physiological variables such as body temperature and blood glucose within optimal ranges. Homeostasis is defined as the collection of physiological processes and behavioral actions that keep the internal milieu of the body steady, or nearly so. The physiological actions of both neural and non-neural tissues contribute to the body's defenses. Through autonomic projections to internal organs, the nervous system influences the state of virtually every organ. The nervous system is particularly important in its unique ability to mount anticipatory or preemptive defenses against changes that could potentially push the body's physiology out of homeostatic range.

The nervous system anticipates threats to homeostasis on several time scales. On an immediate time scale, the sight of food, the intention to stand up, and the like elicit nervous system-mediated reactions that anticipate and prevent the body from deviating from homeostasis. On a daily time scale, the nervous system sets a circadian rhythm that organizes the timing of many physiological processes, such as ingestion, digestion, and hormone secretion. Finally, on a seasonal time scale, homeostatic limits are adjusted to the seasonal environment, so that for example, we feel chilly during the summer at an ambient temperature that is perceived as balmy in winter time.

In this chapter, we first address three commonly held misconceptions about homeostasis. Next, we examine several homeostatic systems: thermoregulation, cardiovascular function, breathing, micturition, and digestion. Finally, we consider sleep and the circadian rhythm.

MANY AREAS OF THE NERVOUS SYSTEM PARTICIPATE IN ANTICIPATORY HOMEOSTASIS

Homeostasis has often been modeled as a servomechanism—in other words, a feedback error correction system like a home thermostat. However, a servomechanism only engages temperature corrections *after* the temperature has deviated from a tolerance zone (Fig. 27-1A). If this were the case in the body, heat loss mechanisms would be engaged only after core temperature rose above a *thermoneutral zone*, whereas heat gain and heat conservation would occur when temperature dropped below the thermoneutral zone. However, unlike our dwellings, our core temperature does not oscillate in and out of our preferred zone, *the thermoneutral zone* (Fig. 27-1B). Instead, core temperature and other physiological variables are maintained within restricted limits primarily by *anticipatory* adjustments. In the example of thermoregulation again, you step out of your dwelling and the temperature is a toasty 95°F (35°C), you start to sweat, vasodilate cutaneous vessels, and breathe faster—all of which are heat loss mechanisms. As a consequence of these rapid adjustments, core temperature is prevented from increasing. Another example of an anticipatory adjustment is the insulin release that *precedes* eating. This is aptly termed the *cephalic phase*, as it requires the brain. As a result of homeostatic defenses, most of which are anticipatory, physiology is remarkably steady across a wide variety of conditions.

A second common misconception about homeostatic regulation is that homeostasis stems entirely from the hypothalamus. Continuing the example of thermoregulation, neurons within the hypothalamus are directly sensitive to temperature, glucose, hormone levels, and many other factors. Although hypothalamic neurons respond to temperature changes with changes in firing rate, hypothalamic temperature does not vary by even 0.5°C across variations in ambient temperature of 40°C–50°C. Even a small change in brain temperature can produce adverse results such as extreme lethargy, confusion, and disorientation indicative of widespread dysfunction. Instead of temperature-sensing occurring in the hypothalamus, thermoreceptive neurons that innervate the skin and the spinal cord sense thermal challenges and initiate physiological and behavioral reactions before the hypothalamus temperature ever changes. The hypothalamus is certainly important to homeostasis and is a key site where hormones act to engage physiological adjustments. The hypothalamus also serves as an integrator for the coordination of different homeostatic systems, so that for example, our thermoneutral zone is at lower temperatures during sleep. Nonetheless, the hypothalamus does not achieve homeostasis solo but rather is one important member of a wide-ranging neural network serving homeostasis.

The third common misconception regarding homeostasis is that homeostatic functions depend entirely on the autonomic nervous system. This is simply not true. Breathing, critical to life, depends primarily on the diaphragm, which is skeletal musculature and under voluntary control. Further, virtually every homeostatic function requires cooperation between somatomotor and autonomic neurons. For example, micturition depends on the contraction of the *detrusor* muscle, a smooth

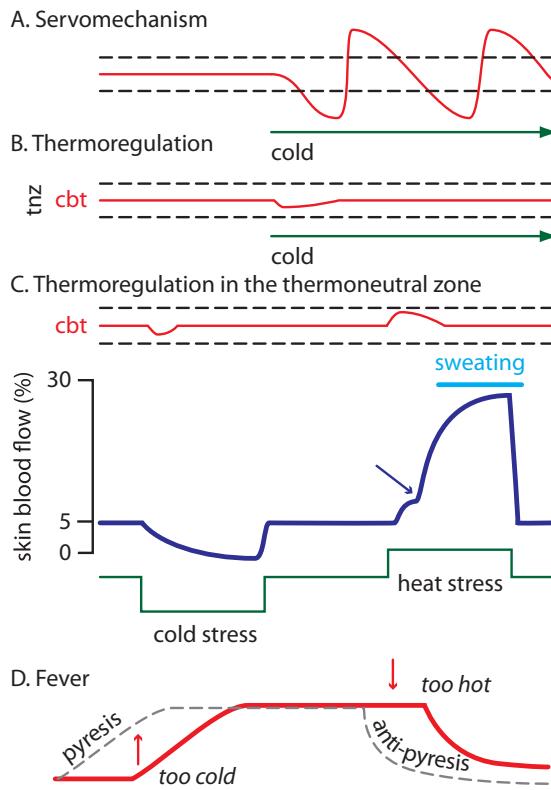


Figure 27-1. A: A servomechanism provides a feedback correction but requires that the regulated variable deviate from the acceptable range. In the thermostat example shown here, the actual temperature (red line) drops below the lower limit of allowed temperatures (dashed lines) and then heat is turned on. The temperature is heated to a value above the upper limit before being allowed to drop again. In this way, temperature oscillates back and forth, above and below the desired temperature. B: Thermoregulation keeps core body temperature (*cbt*, red line) within the thermoneutral zone (*tnz*, dashed black lines). In response to exposure to cold, heat conservation and heat production effectors are engaged, so that core body temperature never deviates from the thermoneutral zone. C: At thermoneutral temperatures, thermoregulation is accomplished by vasomotion. In response to a drop in temperature, skin blood flow (dark blue line) drops from a resting value of about 5% of cardiac output to near zero. Conversely, in response to heat stress, skin blood flow increases. At first the increase is due to a relaxation of active vasoconstriction. If that response is insufficient, an active vasodilation occurs (starting at the inflection point indicated by the arrow). In addition, in response to moderate heat stress, sweating occurs (light blue line). These vasomotor adjustments keep core body temperature (*cbt*, red line) within the thermoneutral zone (dashed black lines). D: During a fever, the set point (dashed gray line) increases in response to a pyrogen. The increase in set point activates heat production effectors, shivering and increased metabolism, and core body temperature (red line) increases, after a delay. While core body temperature is increasing but is still below the set point, the subjective feeling is one of being too cold. When core body temperature reaches set point, the chills subside. When the fever breaks, either naturally or in response to an antipyretic, the set point decreases and heat loss mechanisms, such as sweating and throwing off blankets, are engaged. While core body temperature is decreasing but is still above set point, the subjective feeling is one of being too warm.

muscle controlled by parasympathetic neurons, and the voluntary relaxation of the *external urethral sphincter*, a skeletal muscle.

In sum, the following are principles of homeostatic regulation:

- Homeostatic regulation can be, and often is, anticipatory.
- Neurons throughout the brain, including but not restricted to the hypothalamus, are critical to homeostasis.
- Anticipatory and feedback influences of the brain on the body's physiology can be triggered by either external stimuli, such as temperature, or internal stimuli, such as hormones.

- To effect homeostasis, the brain employs changes in behavior (skeletal muscle), autonomic output (smooth muscle, cardiac muscle, glandular release), and hormonal release.

We now examine several homeostatic systems in some detail.

THE BIGGEST THREAT TO THERMOREGULATION IS OVERHEATING

Thermoregulation is perhaps the easiest homeostatic system to visualize and understand. The goal of thermoregulation is to maintain the body at about 37°C during waking and under normal circumstances. Core temperature is defended against both cold stress, termed *cold defense*, and heat stress, termed *heat defense*. Effectors of cold defense include heat production and heat conservation, whereas *heat defense is accomplished only through heat loss*. There is no mechanism for active cooling. In other words, we can dissipate body heat by sweating, panting, and vasodilation but we lack a physiological *refrigeration* process. Consequently, overheating is a far greater threat to the body than is hypothermia.

THERMOREGULATORY EFFECTORS ARE PRIMARILY SOMATOMOTOR AND SYMPATHETIC

Heat production is accomplished by shivering using skeletal muscle and by increasing metabolic activity and therefore metabolic heat production. The effectors of heat conservation are cutaneous vasoconstriction and postural adjustments that decrease the body's surface area. An example of the latter is a huddling posture. Heat loss is accomplished by sweating, panting, cutaneous vasodilation, and postural adjustments that increase the body's surface area. In addition to the physiological thermoregulatory effectors inherited through evolution, modern humans have added cultural behavioral effectors for thermoregulation. Examples include donning more or less clothing, seeking shelter or covering blankets, turning on an air conditioner or a heater, running through a sprinkler, or building a fire.

The behavioral effectors of thermoregulation—postural adjustments, clothing, and so on—depend on skeletal muscle activity. In addition, skeletal muscles are responsible for shivering and panting to produce and lose heat, respectively. The remaining thermoregulatory effectors—vasomotor changes, metabolic rate, and sweating—are under sympathetic control.

VASOMOTION DEFINES THE THERMONEUTRAL ZONE

The range of the thermoneutral zone is some measurable fraction of a degree Centigrade, roughly 0.4°C ($<1^{\circ}\text{F}$), in the healthy human. The thermoneutral zone is centered at a defended temperature termed the **set point**. As the body temperature varies within the thermoneutral zone, the only thermoregulatory effectors active are vasomotor. Within this range, sweating, panting, shivering, and metabolic adjustments contribute little if at all to determining core body temperature. The range where vasomotion is the only active thermoregulatory effector is the thermoneutral zone (Fig. 27-1C).

Vasomotor effectors can be triggered by changes in core temperature and by local changes in skin temperature. Changes in core temperature are sensed by sensory neurons, processed by the central nervous system (CNS), and lead to changes in sympathetic output. Local changes in skin temperature have direct peripheral effects that lead to either vasoconstriction or vasodilation and *do not require the participation of the CNS*. Mechanisms to alter vasomotion include:

- Noradrenergic sympathetic fibers innervate cutaneous arterioles, and when stimulated, cause vasoconstriction.
- Cholinergic sympathetic fibers innervate cutaneous arterioles in the *glabrous*, or nonhairy, skin. Stimulation of these fibers causes vasodilation.
- Local increases in temperature elicit vasodilation that is mediated by sensory neurons and the local release of nitric oxide.
- In response to local cooling, cold-sensitive sensory fibers facilitate norepinephrine release from sympathetic vasoconstrictor fibers, leading to increased vasoconstriction.

Ultimately, vasomotion changes the blood flow through the skin, either increasing or decreasing blood flow through vasodilation and vasoconstriction, respectively (Fig. 27-1C). The more blood flow at the surface of the body, the more heat is lost to the environment. Thus, the normal operation of thermoregulation works something like the following. As body temperature approaches the lower end of the thermoneutral zone or when skin temperature cools, cutaneous vasoconstriction reduces skin blood flow. The basal level of skin blood flow is about 5% of cardiac output and can go to 0% in response to cold. As body temperature approaches the upper end of the thermoneutral zone or when skin temperature warms, the initial response is a reduction in vasodilation. If the warming persists, active cutaneous vasodilation occurs and this greatly increases skin blood flow to a large proportion of cardiac output. Along with active vasodilation, sweating is triggered, and the combination of vasodilation and sweating is typically effective in preventing overheating. The width and absolute range of the thermoneutral zone differs across age, seasonal temperatures, hormonal status, and a myriad of other factors. For example, the thermoneutral zone of perimenopausal women who suffer from hot flashes is so narrow that it is not measurable (see Box 27-1).

THE THERMONEUTRAL ZONE NARROWS IN PERI- AND POSTMENOPAUSAL WOMEN.

Up to 80% of perimenopausal and postmenopausal women experience hot flushes, hot flashes, or night sweats. Collectively, these three symptoms are referred to as **vasomotor disorders** as they all include an *initial vasodilation event* followed by the sensation of being far too hot and behaviors aimed at reducing core temperature. The best characterized of the vasomotor disorders, a hot flash, is a short-lived, rapid-onset, subjective feeling of being excessively and uncomfortably hot. Physiologically, the first and core event in a hot flash is a spontaneous increase in cutaneous blood flow that is usually accompanied by an increase in heart rate. Within a minute or two of the increase in skin blood flow, women report the subjective sensation of having a hot flash and try to cool off by removing clothes, opening a window, turning on a fan, or the like. After a further lag, sweating, a powerful and rapidly effective heat loss process, starts. Sweating produces a large decrease, typically more than a degree centigrade, in core temperature.

The core temperature of men and nonmenopausal women can vary within a 0.4°C range without eliciting a thermoregulatory reaction. In contrast, in

women with vasomotor disorders, thermoregulatory reactions are elicited *in the absence of any measurable change in core temperature*. This constriction of the thermoneutral zone results in symptomatic menopausal women feeling alternately too cold and too hot. Thus, hot flashes and night sweats are just the most uncomfortable manifestations of a more general dysfunction of thermoregulation in menopausal women.

It should be noted that since testosterone stimulates prostate cell growth, men with prostate cancer receive treatment to reduce testosterone production or to block the effect of testosterone. Most of the men receiving antitestosterone treatment suffer from hot flashes, suggesting that loss of testosterone, like loss of estrogen, leads to hot flashes. Similarly, vasomotor disorders in both men and women are effectively treated by estrogen replacement therapy. Unfortunately, estrogen increases the risk of breast cancer and has uncomfortable side effects in men. Fortunately, the frequency of hot flashes and night sweats diminishes within a year or two of menopause in women or within months of antitestosterone treatment in men.

There is a key vulnerability to the vasomotor system of thermoregulation. Any change in temperature due to vasomotion depends on the transfer of heat between the skin and the environment. At very cold temperatures, below freezing, letting the skin equilibrate to the environment causes **frostbite**. Frostbite can produce permanent changes in skin, circulation, innervation, and bone structure. The first line of defense against frostbite is a paradoxical *vasodilation* to extreme cold. This vasodilation warms the exposed tissue and prevents frostbite, at least for some time. Vasodilation is not effective in individuals with compromised circulation, such as diabetics, who therefore are at a higher risk for frostbite.

At very warm temperatures, there is a strong risk of gaining heat through vasodilation. Warm temperatures, even very warm temperatures, do not elicit vasoconstriction. In other words, there is no paradoxical vasoconstriction at very warm temperatures analogous to the paradoxical vasodilation that occurs at freezing temperatures. For this reason, ambient temperatures above skin temperature and certainly those above body temperature are medical dangers and will lead to death if unchecked. The only effective responses are sweating and relocating to a cooler environment. Consequently, it is a matter of life and death that governments and municipalities set up cooling centers where individuals without access to air conditioning can go during heat waves.

THE SET POINT VARIES ACROSS CIRCUMSTANCES

The center of the thermoneutral zone is the *set point*, an empirically defined temperature that the body defends against change. This set point is very important because the perception of one's temperature is always *in relation* to the set point. For example, a body temperature of 39°C is perceived as mildly hot when, as is true under normal circumstances, the set point is at 37°C. In contrast, when the set point is at 39°C, a body temperature of 39°C does not feel hot. As another example, the set point falls during sleep relative to during waking. This gives rise to the common experience of feeling cold at bedtime but quite warm upon unexpectedly waking up in the middle of a sleep, despite core temperature's being lower during sleep than during waking.

Fever is characterized by an increase in the set point (Fig. 27-1D). A **pyrogen** is a substance that elicits **pyresis**, the medical term for a fever. During the development of pyresis, set point increases before core temperature does. Consequently, febrile individuals feel cold; this corresponds to the familiar chills that foreshadow a fever. During a fever, shivering and an increase in metabolic rate drive core temperature up, toward the elevated set point. **Antipyresis**, referring to a fever breaking, is characterized by a lowering of the set point. Consequently, people feel too warm when a fever breaks.

The concept of a defended set point makes it very important to know the underlying cause of an elevated body temperature. **Hyperthermia** refers to a body temperature that is greater than set point. Hyperthermia often results from excessive environmental heat or overexertion. With the exception of **malignant hyperthermia**, a thankfully rare condition (see Box 27-2), hyperthermia is effectively treated with lots of fluids and active cooling of the body. However, the same treatment for an individual with a fever would simply increase the body's drive to increase core temperature. Therefore, a person with a high fever must be treated with **antipyretic drugs** to bring the set point down (see Box 27-3). Conversely, antipyretics are ineffective in treating a person with hyperthermia. Note that **hypothermia** refers to a body temperature that is below set point. There are no clinical conditions in which set point is clearly lowered. In other words, there is no analogy to fever for a decrease in body temperature. Therefore, hypothermia is always treated by rewarming using progressively more aggressive methods depending on the severity of the drop in core temperature.

THE BAROREFLEX STABILIZES BLOOD PRESSURE ACROSS A SHORT TIME SCALE

A number of tissues regulate or influence cardiovascular function. Notably, the heart, kidneys, adrenal gland, and peripheral vasculature are all important in setting the normative level of blood pressure in an individual.

MALIGNANT HYPERTHERMIA IS A MEDICAL EMERGENCY THAT CAN BE FATAL.

Malignant hyperthermia is a rare reaction to commonly used inhalational general anesthetics such as isoflurane. Mutations in the **ryanodine receptor** are the known cause of malignant hyperthermia. The ryanodine receptor plays an important part of coupling excitation to contraction in skeletal muscles by pairing the influx of calcium ions with a massive release of calcium ions from intracellular stores. The mutations that lead to malignant hyperthermia render the ryanodine receptor more sensitive to calcium ions in the presence of triggering general anesthetics. Thus, calcium ions flood into skeletal muscles, triggering muscle contraction and adenosine triphosphate (ATP) consumption, which in turn lead to excessive heat production.

Malignant hyperthermia was fatal in a majority of cases 50 years ago. Fortunately, today **dantrolene**,

a drug that blocks ryanodine receptor-mediated release of intracellular calcium ion stores, prevents most fatalities from malignant hyperthermia. Nonetheless, malignant hyperthermia is appropriately treated as a serious medical emergency. General anesthetic administration must be discontinued and dantrolene administered immediately.

We usually do not know whether a person is susceptible to malignant hyperthermia before the first “experiment” of general anesthesia is tried. On the other hand, an individual who has been exposed to triggering general anesthetics without showing malignant hyperthermia is considered to be free of a susceptibility mutation. Since malignant hyperthermia runs in families, a careful history may be helpful in identifying potentially susceptible individuals.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS DOUBLE AS ANTIPYRETICS.

Pyrogens lead to the synthesis of prostaglandin E₂ and its release into the *medial preoptic area*, a region in the rostral hypothalamus. The effect of prostaglandin E₂ is to elevate set point. Therefore, drugs that block prostaglandin synthesis, such as aspirin, also prevent or reverse the elevation in set point that defines fever.

The role of the brain in generating long term hypertension remains controversial (see Box 9-4). However, it is incontrovertible that the brain regulates blood pressure across a short time scale of seconds to minutes and even hours. A primary mechanism through which this regulation is accomplished is the **baroreflex**.

The baroreflex is a feedback reflex that serves to stabilize blood pressure in response to increases or decreases. It is essentially the blood pressure version of a stretch reflex. Baroreceptors are primary afferents that sense the pressure (*baro* is Greek for weight) within the carotid sinus and aortic arch. Baroreceptors fire at rest so that the discharge rate of baroreceptors increases when blood pressure increases and decreases when blood pressure decreases. Baroreceptors carry information about blood pressure into the medulla through the glossopharyngeal and vagus nerves and terminate in the caudal portions of the nucleus tractus solitarius (Fig. 27-2). Nucleus tractus solitarius neurons that receive baroreceptive input send this information to neurons in the caudal ventrolateral medulla, which in turn inhibit neurons in the **rostral ventrolateral medulla**, or **rVLM**. Through this circuit, increases in blood pressure cause inhibition of neurons in the rostral ventrolateral medulla, whereas decreases in blood pressure disinhibit rostral ventrolateral medullary neurons.

The rostral ventrolateral medulla is a **sympathoexcitatory** region. This means that stimulation in the rostral ventrolateral medulla increases sympathetic outflow. Neurons in the rostral ventrolateral medulla influence sympathetic activity through direct projections that excite preganglionic sympathetic motor neurons in the intermediolateral cell column of the thoracic cord. The sympathetic effects

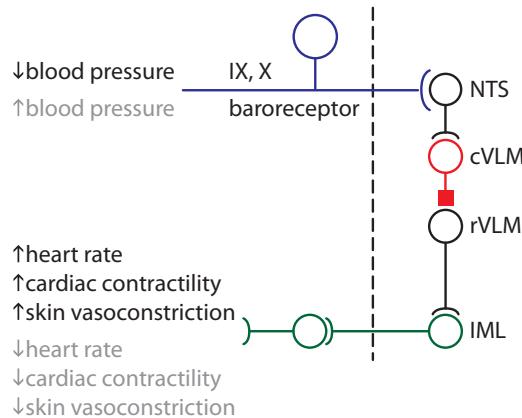


Figure 27-2. The baroreflex serves to dampen changes in blood pressure. Baroreceptors that innervate the carotid sinus and aortic arch enter the nervous system through the glossopharyngeal and vagus nerves (IX, X) and excite cells in the nucleus of the tractus solitarius (NTS). Cells in the nucleus of the tractus solitarius excite cells in the caudal ventrolateral medulla (cVLM), which in turn inhibit cells in the rostral ventrolateral medulla (rVLM). Cells in the rostral ventrolateral medulla are sympathoexcitatory, as they excite preganglionic sympathetic neurons in the intermediolateral cell column of the thoracic cord (IML). Increasing sympathetic outflow increases heart rate, cardiac contractility, and skin vasoconstriction. These three effects lead to an elevation in blood pressure because blood pressure is a function of cardiac output (in turn dependent on heart rate) and peripheral resistance. There is one sign switch in this circuit due to the inhibitory neuron in the caudal ventrolateral medulla. Therefore, a decrease in blood pressure leads to a reflexive increase in blood pressure (black), while an increase in blood pressure leads to a reflexive decrease in blood pressure (gray). Note that the arrangement of neurons in this diagram does not accurately reflect the anatomic relationships between the areas involved.

through which activation of the rostral ventrolateral medulla leads to an elevated blood pressure include increases in heart rate, myocardial contractility, and the peripheral resistance of arterioles.

In addition to the baroreflex, baroreceptor input to the nucleus tractus solitarius also leads to a decrease of heart rate mediated by increasing parasympathetic vagal activity. This vagal reflex response can be initiated by a variety of stimuli, including abdominal pressure, eye pressure, cold water immersion, and breath-holding.

THE BARORECEPTOR REFLEX CAN BE MODULATED

A steady blood pressure may serve us well under many circumstances. Yet, there are conditions when the increase in oxygen and nutrients afforded by an elevation of blood pressure is adaptive. For example, during a fight-or-flight reaction, skeletal muscles are active and are best served by more blood flow. Several mechanisms exist to suppress the baroreceptor reflex so that a greater increase in blood pressure is required to trigger a reflexive adjustment. Noxious input, signals from the hypothalamus related to exercise, feeding, and strong emotions all can lead to baroreceptor reflex modulation. A failure of the baroreceptor reflex can contribute to **orthostatic hypotension** (see Box 27-4).

Hypertension that is not caused by vascular, renal, or cardiac abnormalities is termed **neurogenic**. For example, individuals with obstructive sleep apnea develop neurogenic hypertension. In hypertensive animals and humans, there is an increase

ORTHOSTATIC HYPOTENSION REPRESENTS A FAILURE OF THE BARORECEPTOR REFLEX.

Orthostatic hypotension refers to an episode of low blood pressure associated with standing up. The low blood pressure prevents adequate cerebral blood flow and, consequently, there is a feeling of lightheadedness and people often report seeing spots. If the cerebral blood flow decreases sufficiently, syncope occurs (see Chapter 14). Passively tilting someone from a horizontal to a vertical position does not elicit a hypotensive response, evidence that skeletal muscle contraction plays a role in the pathogenesis of orthostatic hypotension. There are two forms. **Initial orthostatic hypotension** refers to a fall in systolic blood pressure of at least 40 mmHg *within 15 seconds* of standing up. The more common form, called simply orthostatic hypotension, involves a fall in systolic blood pressure of at least 20 mmHg *after 3 minutes* of standing up. The mechanisms of these two problems are very different as are the demographic characteristics of the individuals affected.

Most people have experienced at least a mild form of initial orthostatic hypotension when rising rapidly from a recumbent position or a squat. At least one mechanism contributing to initial orthostatic hypotension is an overactive baroreceptor reflex. Standing up may elicit a precipitous decline in peripheral resistance. In support of this idea,

initial orthostatic hypotension is most severe when an affected individual stands up from a squat. The interpretation of this finding is that the blood vessels are compressed during a squat and that, upon standing up, the large decrease in vascular resistance in the legs allows blood to briefly pool there. The result is a decrease in cardiac output and thus blood pressure. Initial orthostatic hypotension is most common in young, thin people. Educating patients to stand slowly and to deliberately contract their leg muscles helps prevent syncope and potential injury.

The more common orthostatic hypotension, which involves hypotension after 3 minutes of standing, preferentially affects primarily elderly people. There are many causes of orthostatic hypotension that do not involve the nervous system. One of the most common such causes is low blood volume, often secondary to dehydration. In contrast, neurogenic orthostatic hypotension stems from a loss of either central or peripheral norepinephrine in association with for example, Parkinson's disease or **multiple systems atrophy**. Without adequate support from sympathetic outflow, a person cannot maintain adequate cerebral blood flow while in an upright posture. Treatment for orthostatic hypotension is tailored to the underlying cause.

in both sympathetic nerve activity and in the sensitivity of the baroreceptor reflex. A role for the rostral ventrolateral medulla in neurogenic hypertension has been postulated but remains controversial.

INSPIRATION IS THE KEY COMPONENT OF NORMAL BREATHING

Breathing is a patterned somatomotor movement that serves a homeostatic function. The critical skeletal muscles for respiration are under volitional control. Despite our ability to voluntarily take command of respiration, most of the 500 million or so breaths in an 80-year lifespan, even those that occur during wakefulness, are performed without conscious thought.

Breathing has three phases: inspiration, postinspiration, and expiration. Inspiration is accomplished by two pump muscles, the diaphragm and the external intercostal muscles, with the diaphragm playing the critical role. The diaphragm is innervated by spinal motoneurons in C₃–C₅, which send their axons through the **phrenic nerve**. Contraction of the diaphragm expands the thoracic cavity, creating a low-pressure sink into which air floods in (Fig. 27-3A). However, the flow of air is tempered by the resistance in the upper airway. Upper airway resistance is governed by oral and pharyngeal muscles innervated by cranial nerves VII, IX, X, and XII (see Fig. 17-11). Constriction of the upper airway decreases inspiratory volume (see Box 27-5).

Expiration can occur passively as the lungs and thoracic cavity relax back to their starting position. Indeed, during normal breathing, termed **eupnea**, inspiration is followed by the passive recoil of the lungs and there is *no* active expiratory phase (Fig. 27-3B). In other words, as we sit quietly, our breathing consists almost exclusively of periodic contractions of the diaphragm. However, when carbon dioxide (CO₂) production increases, for example during exercise, passive expiration is replaced by active expiration. Essentially, active expiration rids the body of excess CO₂ generated by activity.

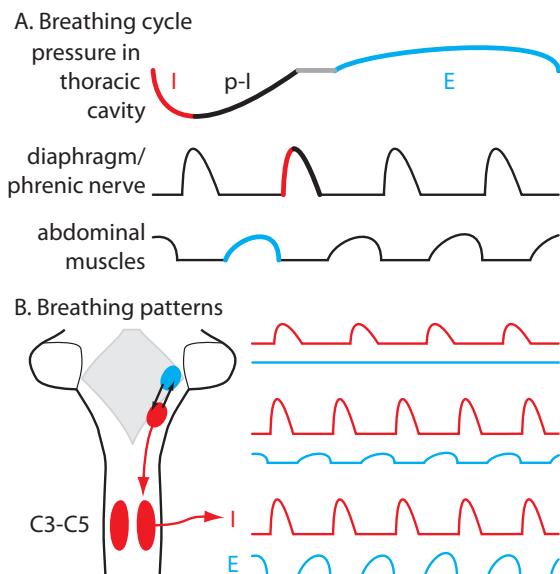


Figure 27-3. A: A single cycle of breathing consisting of inspiratory (I), postinspiratory (p-I), and expiratory (E) phases is shown at the top. The bottom two traces show that inspiration (red) is accomplished by activation of phrenic motoneurons that innervate the diaphragm. Contraction of the diaphragm expands the thoracic cavity and decreases the pressure therein. For quiet breathing, the ribcage recoils to its starting position to support passive expiration. During increased energy expenditure and increased CO₂ formation, active expiration using abdominal muscles occurs (blue), thereby increasing the thoracic pressure and forcing air out of the lungs. B: Eupnea (top pair of traces) consists of inspiration (red) and passive expiration. The pre-Bötzinger complex (red area in brainstem cartoon at left) produces the rhythm required for eupnea. The output of the pre-Bötzinger complex reaches phrenic motoneurons (red area marked C₃–C₅) in the upper cervical cord. Phrenic motoneurons control the diaphragm and produce the basic breathing rhythm. A disconnection between the pre-Bötzinger complex and the phrenic motoneurons in the upper cervical cord renders an individual dependent on a respirator. As energy demands increase (middle pair of traces), respiratory frequency increases, tidal volume increases, and active expiration (blue) occurs. With further energy expenditure, active expiration (E) increases in effort (bottom pair of traces). The breathing rhythm is produced by interactions between the pre-Bötzinger complex and the parafacial respiratory group (blue area). The output of the parafacial respiratory group controls active expiration through projections to the abdominal muscles (not shown).

A COLLAPSE OF THE UPPER AIRWAY DURING SLEEP PRODUCES REPEATED EPISODES OF APNEA.

Upper airway muscles relax during sleep. In some individuals, the upper airway actually collapses during inspiration when the pressure in the airway is lowest. This collapse results in **apnea**, a cessation of breathing. Individuals with **obstructive sleep apnea** can experience hundreds of *apneic* episodes, each lasting 10 seconds to 2 minutes, every night. The accumulated effects of repeated, intermittent apnea are severe. Individuals develop daytime sleepiness, hypertension, and are at high risk for cardiac arrest and stroke.

The first line of treatment for obstructive sleep apnea is to increase the pressure in the airway, either during inspiration alone or during both inspiration

and expiration, using a device such as a **continuous positive airway pressure**, or **CPAP**, device. The CPAP machine has a mask which fits over the patient's mouth, nose, or both. Positive air pressure is maintained within the mask, thus preventing airway collapse.

Obesity, smoking, and diabetes are risk factors for obstructive sleep apnea. As the incidence of obesity and diabetes continue to climb in industrialized societies, so too has the incidence of obstructive sleep apnea. In the United States, 5%–10% of the population suffers from obstructive sleep apnea, much of it as of yet undiagnosed.

SIGHS OCCUR PERIODICALLY AND PREVENT ALVEOLAR COLLAPSE

Gas exchange in the lungs occurs through hundreds of millions of structures called **alveoli** (singular is **alveolus**). The alveoli are hollow spherical formations, about 1 millimeter in diameter. The inside of the alveoli is coated by a monolayer of **surfactant**, which reduces the surface tension on the alveoli. A reduction of alveolar surface tension decreases the work needed to expand the alveoli and achieve gas exchange. However, over time there is a tendency for the alveoli to collapse. When the alveoli collapse, the surface surfactant on the inner surface of the alveoli sticks together and is difficult to separate. Imagine trying to inflate a collapsed water balloon. As this analogy makes apparent, reinflating collapsed alveoli is difficult.

Mammals use the tactic of *preventing* alveolar collapse before it occurs. To do this, we *sigh* about 10–12 times per hour. A sigh is an augmented inspiration, a hyperinflation, which inflates the alveoli by creating a very-low-pressure sink within the thoracic cavity. This periodic superinflation of the alveoli counters the natural tendency for alveolar collapse and prevents **atelectasis**, or lung collapse. Because of the importance of periodic sighing to lung health, artificial respirators are programmed to produce periodic hyperinflations in individuals unable to breathe on their own. It is interesting to note that sighs also appear to serve as a way to express certain emotional states (see Box 27-6).

SIGHS SERVE AS EMOTIONAL SIGNALS.

Sighs not only serve the physiological function of preventing alveolar collapse but also are used and understood as emotional expressions. Sighs are understood by others as expressions of sadness, boredom, weariness, resignation, or as a sign that the sigher finds something stupid or hopeless. Interestingly, people do not always understand sighs as they are intended. Sighs are primarily produced to express resignation or boredom. Both of these emotions reflect a disconnect between expectation and actuality and the acceptance that the disconnect is out of one's control. For example, resignation happens when hopes and desires become unattainable, and people are forced to let them go. Boredom results when one's expectation to be entertained and amused is dashed. Individuals trying to solve very difficult puzzles sigh as they try various solutions that do not work.

As discussed in Chapter 2, we will never know whether a rooster crows because it is happy, or because it wants to wake the hens, or because it hates its neighbor. Similarly, sighs serve a variety of physiological and emotional functions and, at present, it is not possible to distinguish a sigh to prevent alveolar collapse from one that expresses resignation or relief, and so on.

BREATHING IS PRODUCED BY A CENTRAL PATTERN GENERATOR IN THE MEDULLA

Fundamentally, eupnea consists of a repeated pattern of bursting activity in the phrenic nerve that leads to periodic contraction of the diaphragm and external intercostal muscles and associated changes in upper airway muscles that modulate the patency of the airway. This fundamental pattern is produced by a central pattern generator network in a small region of the ventrolateral medulla known as the pre-Bötzinger complex (Fig. 27-3B). The pre-Bötzinger complex sends out a pattern of activity to motoneurons in cranial nerve nuclei and the spinal ventral horn. Essentially, the pre-Bötzinger complex is the source of the breathing rhythm, and probably of sighs, during eupnea. Damage to the pre-Bötzinger complex itself may result in disordered breathing specifically during sleep (see Box 27-7).

Injury to the spinal cord above the level of phrenic motoneurons, meaning in either C1 or C2, may, depending on the location and extent of the lesion, disconnect the pre-Bötzinger complex and the phrenic motoneurons in the upper cervical cord. The consequence of such disconnection is paralysis of either half or all of the diaphragm. People with high cervical spinal cord injuries typically need ventilator assistance at the very least, and some become dependent on a respirator for life. Spinal cord injuries as low as the high thoracic cord lesion the brainstem connections to external intercostal muscles, with adverse consequences on breathing.

BREATHING IS MODULATED BY THE LEVELS OF OXYGEN AND CARBON DIOXIDE IN THE BLOOD

Eupnea serves us and other mammals well as long as we are resting quietly and remain unstressed by environmental factors such as heat. However, during activity or in challenging environments, energy demands increase, and as a result, the body needs more oxygen. During exertion, as we use our muscles or increase metabolic rate, the production of CO₂ also increases. Breathing changes to accommodate the needs to inspire more oxygen and to eliminate the buildup of CO₂. Deeper and more rapid inspirations bring in more oxygen (Fig. 27-3B). Moreover, active expiration replaces passive expiration and is able to eliminate the excess CO₂.

Active expiration depends on a second central pattern generator distinct from that in the pre-Bötzinger complex. The central pattern generator critical to active expiration is found just medial to the facial nucleus, in a region which we will call the **parafacial respiratory group** (Fig. 27-3B). Neurons in the parafacial respiratory group are sensitive to the concentration of CO₂. Elevated levels of CO₂ directly activate neurons in the parafacial respiratory group, with the result that active expiration begins. There is parsimony in this arrangement. Exertion is

LOSS OF NEURONS IN PRE-BÖTZINGER COMPLEX LEADS TO DISORDERED BREATHING DURING SLEEP.

Experiments in animals show that the first consequence of damage to the pre-Bötzinger complex is apnea during rapid eye movement (REM) sleep. After more time, apneic episodes start to occur during non-REM sleep. In both Parkinson's disease (see Box 25-7) and amyotrophic lateral sclerosis (see Box 23-1), there is pathological evidence for a loss of neurons in the region of the pre-Bötzinger complex.

In both of these diseases, breathing is disordered during sleep but not during waking. The loss of neurons in the pre-Bötzinger complex may in fact cause a disruption of breathing specifically during sleep. Accumulated damage from a lifetime of random insults and cell deaths may reduce the number of neurons in the pre-Bötzinger complex and contribute to the high incidence of **sleep apnea**.

accompanied by active expiration, mediated by the parafacial respiratory group. Should the active expiration be insufficient to reduce CO₂ concentrations, or should the engagement of the parafacial respiratory group fail for some reason, there is a backup plan. The automatic engagement of active expiration when inadequate ventilation results in a buildup of CO₂ is particularly important during sleep. Individuals with a congenital insensitivity to CO₂ are severely affected, and many require artificial ventilation during sleep (see Box 27-8).

The inspiratory rhythm generated by the pre-Bötzinger complex and the active expiration generated by the parafacial respiratory group are coordinated. Projections between the two central pattern generator networks accomplish this coordination (Fig. 27-3B).

MUSCLES USED FOR BREATHING ARE SHARED WITH MANY OTHER MOTOR PATTERNS

Although breathing may have first dibs on the diaphragm, external intercostal muscles, and muscles of the upper airway, many other motor patterns use at least some of the same muscles. During nonbreathing movements, muscles shared with breathing are controlled by a combination of reconfigured breathing central pattern generators and other central pattern generators specific to nonbreathing movements. For example, there are many different breathing patterns such as gasping, sighing, breathing at different rates, and so on. A reconfiguration of the respiratory central pattern generators in the pre-Bötzinger complex and the parafacial respiratory group are adequate to produce these different breathing patterns. This is analogous to the manner in which reconfigurations of the mesencephalic locomotor region produce walking, trotting, running, and sprinting (see Chapter 22). Coughing is a motor pattern that largely relies on a reconfiguration of the breathing

CONGENITAL CENTRAL HYPOVENTILATION SYNDROME RESULTS FROM THE FAILURE OF CO₂-SENSITIVE NEURONS TO DEVELOP IN THE PARAFACIAL RESPIRATORY GROUP.

Congenital central hypoventilation syndrome, also called **Ondine's curse**, is a genetic disease that is caused by either expanded trinucleotide repeats, as in Huntington's disease (see Box 25-8), or missense mutations in one allele of the gene for a homeobox factor, *PHOX2B*. Homeobox genes are critical to patterning the developing embryo, and the loss of *PHOX2B* specifically causes a failure of CO₂-sensitive neurons in the parafacial respiratory group to develop. Additional neuronal populations that contribute to homeostatic function, such as neurons of the enteric nervous system, also fail to develop. Nonetheless, the breathing abnormalities associated with congenital central hypoventilation syndrome are the most striking and most debilitating aspect of congenital central hypoventilation syndrome.

Individuals with congenital central hypoventilation syndrome are insensitive to elevated levels of CO₂. They therefore are insensitive to asphyxiation. They have a very difficult time exercising as they are unable to detect inadequate ventilation and make appropriate breathing adjustments. The inability to

detect elevated levels of CO₂ requires that artificial ventilatory assistance be employed during sleep. The restrictions on normal life experienced by individuals with congenital central hypoventilation syndrome dramatically illustrate the debilitating effects of an inability to sense CO₂ and highlight the everyday importance of this neural function.

Recall that the onset of Huntington's disease is earliest and disease progression is most rapid in patients with the greatest number of trinucleotide repeats in *huntingtin*. Similarly, it appears that the number of trinucleotide repeats in *PHOX2B* determines age of onset and severity of congenital central hypoventilation syndrome. Thus, an adult with a borderline number of trinucleotide repeats may be largely symptom-free but his or her offspring may have a more classic presentation of respiratory inadequacy at birth. This scenario suggests that it is worthwhile to clinically evaluate the parents of a baby with congenital central hypoventilation syndrome.

central pattern generators with a small contribution from other areas. Motor patterns more distinct from than similar to breathing include swallowing, speech, vomiting, gagging, and sneezing. In these cases, additional central pattern generators work with the breathing pattern generators to suspend breathing during incompatible movements such as vomiting.

URINE STORAGE DOMINATES OUR LIVES BUT BLADDER-EMPTYING MUST OCCUR REGULARLY

We store urine in our bladder for virtually 100% of our lives. Bladder-emptying requires little time, rarely longer than 10 seconds and occupies well under 1% of our lifetime. Nonetheless, the bladder must be emptied regularly. Urinary retention is a medical emergency and can be fatal.

Although critical to survival, micturition is incapacitating in the sense that it prevents an individual from making other movements. It is probably for this reason that forebrain control over the timing of micturition has evolved in most territorial mammals. Modern humans utilize the control circuits inherited from evolution and marry them to social norms, so that the switch from urine storage to micturition occurs at a socially appropriate time and place. The failure to void in accordance with social norms, **incontinence**, has devastating effects on both an affected individual and on his or her loved ones.

In adults, control over the timing of micturition is accomplished by the medial prefrontal cortex. The prefrontal cortex tonically suppresses micturition in accordance with social and environmental conditions. Strokes in the medial orbitofrontal cortex often produce urinary incontinence that is accompanied by a bizarre lack of concern on the part of the patient over the inappropriate voiding.

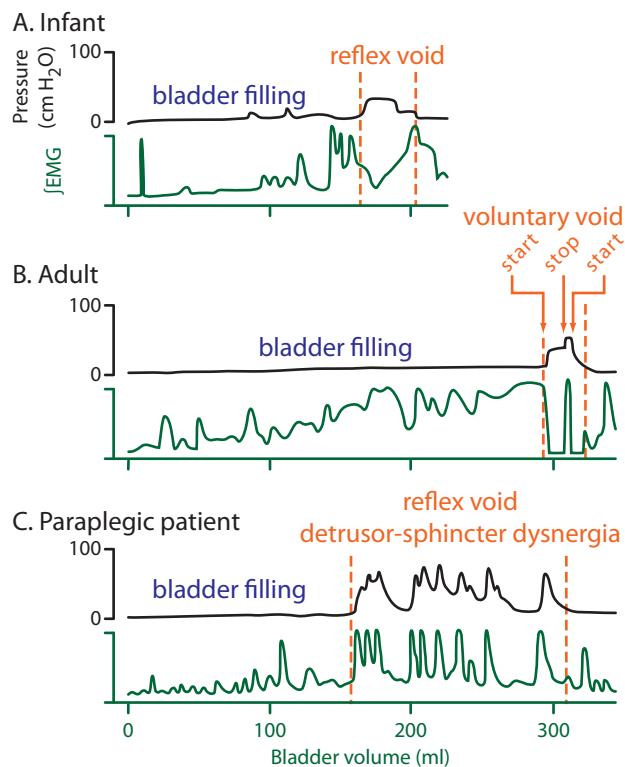
BLADDER CONTROL DEPENDS ON THE COORDINATED ACTIVITY OF VOLUNTARY AND SMOOTH MUSCLES

Afferent input from the bladder that signals bladder filling reaches both sacral circuits that are in immediate control of the bladder and higher centers responsible for initiating voiding at appropriate times. Using information about bladder distension, prefrontal cortex does not engage the pontine micturition center when the bladder is empty. When the bladder fills and micturition is released from inhibition by the forebrain, neurons in the **pontine micturition center** are activated. The pontine micturition center, located just caudal to the periaqueductal gray, is essentially a central pattern generator for micturition. Neurons in the pontine micturition center project to the sacral cord where they contact (1) preganglionic parasympathetic neurons that innervate the *detrusor* muscle, and (2) inhibitory interneurons that contact the motoneurons that innervate the external urethral sphincter. The effect of pontine micturition center activity is (1) detrusor contraction and (2) external urethral sphincter relaxation. This allows urine to flow out of the bladder (Fig. 27-4A-B). It should be noted that although the preganglionic parasympathetic neurons may be influenced by descending inputs, the detrusor muscle cannot be controlled voluntarily. Thus, the voluntary control over voiding occurs at the level of the external urethral sphincter muscle.

Since micturition requires a start signal from the pons, spinal cord injury greatly impairs micturition. In patients with spinal cord injuries in which the connection from the pontine micturition center to the sacral cord is cut, a disordered activation of both the detrusor *and* the external urethral sphincter results (Fig. 27-4C). Essentially, the entire reflex changes, so that upon filling, increases in bladder afferent input result in excitation of both the detrusor and the external urethral sphincter. Although leakage may occur under these circumstances, normal micturition does not. This is termed **bladder-sphincter dyssynergia** and represents a significant problem for spinal cord-injured patients.

Figure 27-4. Three different patterns of human micturition are shown. The top trace in each panel shows the pressure within the bladder that is exerted on the detrusor muscle (which forms the wall of the bladder). The bottom trace is an electromyograph (EMG) trace from the external urethral sphincter. A: Infants do not have forebrain control over voiding. They void purely by reflex. Thus, when the detrusor pressure reaches a threshold level, the infant voids. Note that the infant does not fully relax the sphincter during voiding. B: Healthy adults void under voluntary control. Moreover, adults can start and stop a void by voluntarily relaxing and contracting the external urethral sphincter. Thus as the bladder fills, activity in the urethral sphincter increases until the subject willfully relaxes it (*start*), thereby initiating a void. C: In a patient with spinal cord injury, the detrusor and the external urethral sphincter are contracted simultaneously. The result is that the bladder pressure is increased but the outflow is blocked. This phenomenon is termed detrusor-sphincter dyssynergia and requires medical intervention.

Adapted from Fowler, C.J., Griffiths, D., and de Groat, W.C. The neural control of micturition. *Nature Rev Neurosci* 9: 453–66, 2008, with permission of the publisher, Macmillan Publishers Ltd.



THE ENTERIC NERVOUS SYSTEM IS A LITTLE NERVOUS SYSTEM UNTO ITSELF

The enteric nervous system comprises roughly 200–600 million neurons located in the lining of the gut. It is influenced and in turn influences CNS function. This remarkable nervous system within the gut is able to generate the gut motility and secretions needed for digestion. The enteric nervous system is able to function nearly independently because it consists of sensory neurons, motor neurons, and interneurons. This is in stark contrast to the sympathetic and parasympathetic divisions of the autonomic nervous system, which only consist of preganglionic and postganglionic motor neurons.

The neurons and glia of the enteric nervous system are grouped into thousands of small ganglia distributed along the length of the gastrointestinal tract. Most neurons are odd looking by CNS standards and have appearances more like invertebrate neurons than central vertebrate neurons. For instance, although some enteric cells have a prominent axon, others have processes that resemble invertebrate processes in that they are neither axons nor dendrites.

A prominent feature of the enteric nervous system is the multitude and diversity of neurotransmitters including acetylcholine, γ -aminobutyric acid (GABA), and serotonin (see Box 27-9). In addition, there are a multitude of peptides, many of which were first identified in the gut before eventually being found in the brain. Enteric neuropeptides include cholecystokinin, vasoactive intestinal peptide, neuropeptidene, bombesin, galanin, and substance P, all of which are also present in the brain.

The enteric nervous system allows the gut to function largely independently of the CNS. There are two major locations of enteric neurons:

- *Auerbach's or myenteric plexus*: these cells sit between the outer layer of longitudinal muscles and the middle layer of circular muscles and are present throughout the gastrointestinal tract from the esophagus to the internal anal sphincter.
- *Meissner's or submucosal plexus*: these cells sit between the middle layer of circular muscles and the inner mucosa and are present only in the small and large intestines.

Box 27-9

THE ENTERIC NERVOUS SYSTEM IS SENSITIVE TO TREATMENT WITH SPECIFIC SEROTONIN REUPTAKE INHIBITORS.

One population of enteric cells, the **enterochromaffin cells**, contains over 95% of the serotonin found in the body! When excited by intraluminal pressure, enterochromaffin cells secrete serotonin, which then initiates peristalsis. Because of the involvement of serotonin in the control of peristalsis, it is not surprising that selective serotonin reuptake inhibitors (SSRIs) have effects on gastric motility. At low doses or early in therapy, SSRIs augment serotonergic transmission, resulting in increased peristalsis and diarrhea. At higher doses or later in the therapy with SSRIs, there is a desensitization of serotonin receptors. As a result, constipation occurs.

As may be obvious from their different locations, these two plexi have different functions. The myenteric plexus controls gut motility and the submucosal plexus controls secretions into the lumen of the gut.

Connections between the CNS and the enteric nervous system are bidirectional. Anatomically, axons bringing information from the gut to the CNS outnumber axons taking information from the CNS to the gut by 10:1. Information *from* the gut is used to sense distension, satiety, nausea, and so on. Although relatively few in number, connections from the CNS to the gut can exert powerful control over the enteric nervous system. The vagus nerve innervates and has the greatest influence on movements of the esophagus and stomach and little influence over intestinal and colonic motility. Sympathetic nerves innervate the lower gastrointestinal tract and influence both motility and secretion.

There is a range of patterns of gut motility. The most common is **peristalsis**, the propulsive movement of lumen contents toward the anus that is associated with normal digestion. Other motility patterns include mixing, the **peristaltic rush** that rapidly propels noxious contents toward the anus, and the backward peristalsis that accompanies vomiting. The **interstitial cell of Cajal** is a **pacemaker** cell, meaning that it fires rhythmically on its own. It is the rhythmic discharge of the interstitial cell of Cajal that largely drives gut peristalsis. In the absence of enteric cells, the gut is hypomotile (see Box 27-10).

Secretory reflexes of the enteric nervous system are responsible for returning about 9 liters, more than 2 gallons, of water to the lumen of the gastrointestinal tract each day. The sympathetic nervous system can influence the amount of water secreted. This is one pathway through which emotion, via an effect on sympathetic outflow, may play out in the motility of our guts, a common experience.

Box 27-10

A FAILURE OF ENTERIC NERVOUS SYSTEM DEVELOPMENT CAUSES NEONATAL CONSTIPATION.

The most common disorder of the enteric nervous system is **Hirschsprung disease**, also termed **megacolon** or **congenital aganglionic megacolon**. Hirschsprung disease results when neural crest cells fail to migrate into the distal colon. The severity of the disease is dependent on how much of the colon is **aganglionic**, meaning lacking collections of enteric neurons. Newborns with this problem present with constipation and are typically treated surgically. The normal part of the colon is pulled down and sewed over the aganglionic portion. In many cases, this procedure resolves the problem. In others, careful dietary management is needed for life.

SLEEP IS CLEARLY A BIOLOGICAL NECESSITY, EVEN IF WE DO NOT UNDERSTAND ITS FUNCTION

Sleep can be characterized as a reversible state of decreased mobility and decreased sensitivity to external stimulation. Sleep is an innate behavior that does not require learning. Depriving an animal or person from sleeping by keeping them awake increases the pressure to sleep, often termed *sleep drive*. Extended sleep deprivation has serious adverse consequences, including death if prolonged long enough. The finding that animals throughout phylogeny from flies to fish to mammals exhibit a sleep-like state, show evidence of sleep drive, and are adversely affected by sleep deprivation leads to the conclusion that *sleep is a necessary process*. This firm conclusion is unaffected by our continued inability to answer the “Why do we sleep?” question. It may be that the question is more misguided than instructive.

Sleep is consolidated, so that it occurs at night time in humans and other diurnal animals. The consolidation of sleep is accomplished by interactions between the drive to sleep and a process that links wakefulness to the circadian daytime. The idea is that sleep drive builds during the day and dissipates during a night spent sleeping. Opposing the sleep drive is a circadian facilitation of wakefulness during the daytime hours. A simple, probably familiar, example can illustrate the way in which the opposing processes interact. After spending all night writing a paper or studying for an exam, morning arrives. Because the night before was not spent sleeping, the sleep drive is strong. Yet, the sleep drive is mitigated by the circadian drive to be awake in morning time. Of course, the outcome of these dueling physiological processes varies across individuals, age, and context.

ADULT HUMAN SLEEP CONSISTS OF TWO FUNDAMENTALLY DIFFERENT STATES

Humans and most other mammals exhibit two very different types of sleep: *rapid-eye-movement sleep*, also called *REM*, *paradoxical sleep* or *active sleep*; and *non-REM sleep*, also called *slow-wave sleep*. Because sleep states are difficult to judge by behavioral observations alone, the differences between non-REM and REM sleep are determined and described in electrophysiological terms by the amount of activity in neurons of the cerebral cortex, postural muscles, and extraocular muscles.

The *electroencephalogram*, or *EEG*, measures *synchronized* activity in the cerebral cortex. As cells fire more and more synchronously, the EEG grows in amplitude. During non-REM sleep, cortical neurons are synchronously active, so that the EEG shows slow rhythmic oscillations at a rate of about 1–4 Hz; these

oscillations are termed **δ waves**. When the cerebral cortex shows δ waves, it is unresponsive to outside stimulation. Because many neurons are all firing at the same time during non-REM sleep, EEG recordings have a characteristic *high-amplitude, low-frequency* appearance.

During wakefulness, neurons respond to outside stimuli and fire asynchronously. This results in a distributed pattern of activity and a low-amplitude EEG. During REM sleep, most regions of cortex look “awake.” However, the hippocampus is different from other areas of cortex as it shows synchronized activity that appears as 4–8 Hz **θ waves**. Some postulate that hippocampal θ waves play a role in memory consolidation during sleep, but this intriguing idea remains controversial.

During sleep, there is a paucity of voluntary movements. Humans usually sleep in a recumbent position, and the lack of activity in physiological extensors is particularly accentuated during sleep. During non-REM sleep, there is some, but certainly a minimal amount, of muscle activity. The amount of muscle activity, revealed by electromyograph (EMG) recordings (see Box 21-6), decreases across time as sleep deepens. During REM sleep, the EMG becomes virtually flat, reflecting **atonia**, a total lack of muscle activity. Associated with this atonia is a profound hyperpolarization of motoneurons that greatly increases the threshold needed to activate these neurons. Interspersed within the period of atonia are brief muscle twitches that differ dramatically from organized voluntary movements. REM sleep is, as its name suggests, characterized by rapid eye movements that can be measured with an **electrooculogram**, or **EOG**, that measures extraocular muscle activity. Rapid eye movements are associated with the occurrence of *dreaming*, but dreaming also occurs during non-REM sleep. As a rule, rapid eye movements rarely occur during non-REM sleep. The concurrence of most dreaming with atonia during REM sleep prevents us from acting out our dreams (see Box 27-11).

Box 27-11

IN RAPID EYE MOVEMENT (REM) SLEEP BEHAVIOR DISORDER, ATONIA DOES NOT OCCUR.

Rapid eye movement sleep behavior disorder is a bizarre condition characterized by the absence of muscle atonia during REM and the consequent acting out of dreams. Patients are typically middle aged or older men. During REM sleep, they make loud and angry vocalizations that are usually quite distinct from their waking demeanor. Since patients kick, punch, and flail about, a common problem is injury to a sleeping partner. The dreams that patients act out are almost universally antagonistic, with the patient typically on the receiving end of an attack. Note that REM sleep behavior disorder is entirely distinct from **sleepwalking**. Sleepwalking is

a relatively benign condition that occurs during non-REM sleep.

The atonia during REM is produced by brain-stem networks. Neurons in the medullary reticular formation inhibit motoneurons to produce atonia. In REM sleep behavior disorder, the medullary neurons are not activated and consequently do not inhibit motoneurons to produce atonia. REM sleep behavior disorder shares significant comorbidity with Parkinson’s disease and several other neurodegenerative diseases, suggesting that it may be an early sign of neurodegeneration.

The sleep drive exerts independent pressures for non-REM and for REM sleep. This means that a lack of non-REM sleep from a lost night's sleep will trigger a demand for a compensatory increase in non-REM sleep. Similarly, a lack of REM sleep, even if the full complement of non-REM sleep was obtained, leads to additional REM sleep during the next sleep period.

BRAINSTEM AND FOREBRAIN REGIONS INTERACT TO PRODUCE ALTERNATING STATES OF SLEEP AND WAKEFULNESS

Many brain regions participate in various aspects of sleep–wake regulation. The hypothalamus is a key area, and damage to the hypothalamus can produce either a fatal insomnia or a state of continuous sleep, termed **somnolence**. Neurons in the **posterior hypothalamus**, basal forebrain (see Box 7-1), and histaminergic **tuberomammillary nucleus** all promote wakefulness. Conversely, activity in neurons within the **ventral lateral preoptic nucleus** of the anterior hypothalamus leads to sleep, in part by inhibition of the regions that promote wakefulness. The brain region or regions that mediate sleep drive remain unclear. Yet, widespread cortical excitation, as occurs in response to stimulants such as caffeine or amphetamine, dampens the sleep drive. Conversely, widespread cortical inhibition, as occurs in response to hypnotics such as benzodiazepines, facilitates the sleep drive.

SLEEP STATES OCCUR IN A PREDICTABLE SEQUENCE

Sleep follows a stereotypical pattern, which is termed **sleep architecture**. Sleep begins with light stages of non-REM sleep that progress into stages of increasing EEG synchrony (Fig. 27-5). *REM sleep is only entered into from non-REM sleep* in the healthy individual (see Box 27-12). A normal night of sleep involves four to six cycles of non-REM sleep to REM sleep (Fig. 27-5). In each succeeding cycle, non-REM sleep becomes progressively more synchronous and then switches into REM sleep for 5–10 minutes. Within a single night's sleep, there is more EEG synchrony during the initial few hours and far less by morning. This gradual reduction in EEG synchrony and amplitude from the evening to the morning is associated with a decrease in sleep drive.

Insomnia is among the most common and also heterogeneous health-related complaints. Individuals with insomnia may have difficulty initiating sleep, staying asleep, or may have unsatisfying sleep. Unsatisfying sleep is usually associated with less EEG synchronization than normal and a multitude of arousals each night.

Associated with different sleep stages are consistent changes in homeostasis. For example, gastric motility increases during sleep. There is a decrease in the

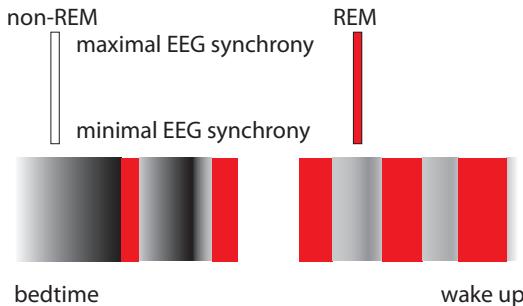


Figure 27-5. A typical night of sleep includes several cycles of non-rapid eye movement (*non-REM*) and REM sleep (*red*). Non-REM sleep has four stages that vary from light (*white*) to deep (*black*). Upon going to bed, drowsiness segues into light non-REM sleep and then sleep deepens progressively. After 90–120 min, a short, 10-min or so, REM episode occurs. This non-REM to REM cycle repeats through the night. At each successive cycle, the time spent in deep sleep decreases, and the time spent in REM sleep increases.

temperature set point during non-REM sleep and thermoregulation is *turned off* during REM sleep. Luckily, we do not spend much time in REM sleep, and so body temperature is in free-fall for a minimum of time. There are also consistent changes in cardiovascular function and breathing. During sleep, certain behaviors, such as voiding, are not supposed to happen. Many patients experience the failure of a homeostatic process during nighttime sleep before any daytime symptoms appear. For example, people with urinary incontinence due to a stroke often have nighttime enuresis long before losing control over voiding during the daytime.

THE SLEEP–WAKE CYCLE IS SYNCHRONIZED TO THE CIRCADIAN RHYTHM

Given that we need to sleep and that sleep is a vulnerable state, the most adaptive organization of sleep and wake would be to consolidate sleep during periods when food availability is lowest and to be most refreshed, awake, and active when food and mates are obtainable. Indeed, the normative pattern for adult humans is to sleep in a single bout of 6–10 hours. Recall from Chapter 16 that neurons in the *suprachiasmatic nucleus* receive information about light levels from photosensitive retinal ganglion cells and behave like an internal clock. Even in the absence of any light cues, we keep a nearly 24-hour sleep–wake cycle. Damage to the suprachiasmatic nucleus abolishes this internal clock.

Connections from the suprachiasmatic nucleus to sleep-regulating regions of the hypothalamus entrain sleep–wake cycles to light–dark cycles. At night, the lack of light leads, via the suprachiasmatic nucleus, to the release of melatonin from the pineal gland. Because the circadian facilitation of wakefulness is entrained by light stimulation, repeated exposure to light during the evening will delay the melatonin increase and prolong the influence of the circadian facilitation of wakefulness. Thus, sleepiness is postponed. On the other hand, reducing light exposure in the evening or increasing light exposure in the morning will produce a desire for an earlier bedtime. It is also possible to directly manipulate circadian regulation using melatonin and melatonin receptor agonists.

By entraining sleep–wake cycles to the entirely predictable circadian rhythm, changes in homeostatic physiology can be made in *anticipation* of waking. Reliably, before we wake up, core temperature, sympathetic nerve activity, and cortisol release increase while gut motility decreases. These changes in physiology enable us to

NARCOLEPSY IS CHARACTERIZED BY ENTRY INTO RAPID EYE MOVEMENT (REM) SLEEP FROM WAKEFULNESS.

Narcolepsy is a sleep disorder characterized by daytime *sleep attacks* that involve a transition from wakefulness to REM sleep, a transition that is not observed in healthy individuals. The cardinal features of narcolepsy are extreme daytime sleepiness and sleep attacks during the day. Sleep attacks are accompanied by a loss of muscle tone, termed **cataplexy**, which can cause injury to the patient. Fragmented sleep at night and hallucinations upon falling asleep or waking from sleep are frequent symptoms. In addition, atonia, which normally only accompanies REM sleep, can occur upon falling into non-REM sleep or waking from sleep. This produces a frightening sensation of being aware, in a drowsy kind of way, but unable to move.

Insight into the circuits governing wakefulness, REM sleep, and atonia derive from the identification

of mutations that cause narcolepsy in dogs. The mutations identified are in a receptor for a neuropeptide, **orexin**, which is at higher levels during wakefulness than during sleep. Although mutations in the gene responsible for narcolepsy in dogs are not found in humans with narcolepsy, the pathophysiology is shared in the sense that humans with narcolepsy have low levels of orexin and a loss of hypothalamic neurons containing orexin. Thus, a deficiency in orexin signaling appears to be a common cause of narcolepsy in dogs and humans. Human narcolepsy may be an autoimmune disorder as it is far more prevalent in people with a particular histocompatibility profile. Treatment is aimed at reducing daytime sleepiness and preventing cataplexy.

perform voluntary actions, perceive the world, and be cognitively alert. What more could one ask for?

THE INSIGHTFUL AND INSPIRED OBSERVATIONS OF A PHYSICIAN LED TO OUR MODERN UNDERSTANDING OF SLEEP AND WAKE REGULATION

Long before the modern interest in sleep, before EEG recordings or the discovery of REM sleep, Constantin von Economo had the revolutionary idea to search for the neuroanatomical locus of sleep. von Economo was a Romanian of Greek descent who practiced psychiatry and neurology in the early 20th century. In 1916, he saw 15 patients whose symptoms did not fit into any known disease at the time. Nor were the complaints of these patients uniform. One group of patients slept too much and exhibited ptosis, another group could not sleep, and the third group did not move.

From carefully examining a modest number of patients, von Economo described three forms of **encephalitis lethargica**: (1) an ophthalmoplegic form associated with hypersomnolence, (2) a hyperkinetic form associated with insomnia, and (3) an

akinetic form that we now term **post-encephalitic parkinsonism**. von Economo did not stop at simply describing three clinical syndromes. He carefully studied the brains of patients. By combining his pathological observations with his meticulous clinical analysis, von Economo was able to postulate: (1) a sleep region in the anterior hypothalamus and (2) a waking region at the midbrain-diencephalic border.¹ Lesion of the former area would produce insomnia. Damage to the latter area would produce somnolence and oculomotor deficits due to involvement of rostral portions of the oculomotor complex.

Remarkably, von Economo's insights have largely been borne out by modern research. It should be noted that encephalitis lethargica has disappeared since von Economo's time. Thus, long after the disease that occupied so much of his career has vanished, von Economo lives on because of his remarkable contributions to our understanding of the biological basis of sleep and wake.

The story of von Economo and encephalitis lethargica is intended to demonstrate the importance of the inquisitive physician to the advancement of our understanding of the brain. Each patient represents a unique combination of history, physiology, genetics, and anatomy asking for help and offering up individual traits to the physician to use as tools. The alert and curious physician holds the potential to help patients while also advancing medicine, and indeed biology, forward just as von Economo did.



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¹ As an aside, von Economo even linked the akinetic form of encephalitis lethargic to damage in the substantia nigra.

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SECTION 7: YOU AND THE BRAIN

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CHAPTER 28

THE BRAIN IN A PHYSICIAN'S LIFE

If you are actually reading this chapter, you have worked hard and engaged with the nervous system. You have read, thought, and talked about the nervous system. Conversations about “myasthenia gravis,” “sodium channel inactivation,” “outer hair cells,” and a myriad of other topics are now understandable to you. For those of you who began reading this book knowing nothing about the nervous system, I recognize how much you have learned, and I hope you do too. And for those of you who knew quite a bit before reading a page, my hope is that you have deepened both your knowledge and interest. You all deserve congratulations for your respective accomplishments.

YOUR KNOWLEDGE OF NEUROANATOMY ALLOWS YOU TO IMAGINE THE LOCATION AND SIZE OF BAUBY'S LESION

We started this course by considering the tragic case of Jean-Dominique Bauby. With your acquired knowledge of neuroanatomy, you can now reconstruct Bauby's lesion. What Bauby tells us in his book is that he had a pontine lesion. Indeed, a pontine stroke is the typical cause of the locked-in syndrome.

How does a pontine stroke explain Bauby's symptoms? Bauby's most striking symptom was the inability to willfully move or speak. This stems from a lesion of the corticospinal and corticobulbar tracts traveling through the basis pontis. Bauby also became deaf in his left ear as a result of his stroke. The only central lesion with that effect is one which knocks out the cochlear nuclei on one side. Bauby also suffered from paresthesia of his body and face, a positive sign indicating a lesion of the ascending sensory tracts bilaterally. The stroke must have damaged portions of the midbrain too, to explain Bauby's nearly total ophthalmoplegia and right mydriasis or blown pupil.

Bauby also suffered from hyperacusis, likely the result of facial nucleus damage. It is striking that Bauby “writes” more about hyperacusis than he complains that he cannot walk. Hyperacusis *demands* Bauby's attention. Bauby's inability to walk is a constant that fades into the background and about which he writes little that is

specific. Bauby's describes hyperacusis as, "... My left ear amplifies and distorts all sounds farther than ten feet away. When a plane tows an ad for the local theme park over the beach, I could swear that a coffee mill has been grafted onto my eardrum... [even] more disturbing is the continuous racket that assails me from the corridor whenever they forget to shut my door... [sending] out an auditory foretaste of hell."

It is also important to consider what is working well in Bauby. Bauby has no deficits in olfaction, vision, sleep, circadian rhythm, memory, language, thought, or executive function. He certainly demonstrates a remarkable consideration for others, exhibiting as much or more concern for the minor inconveniences of others than for his own plight.

DID BAUBY EXPERIENCE DAMPENED EMOTIONS?

Finally, what about Bauby's emotional range? Bauby certainly had intact forebrain circuits that are important for affect and motivation—cingulate, insular, and prefrontal cortices, the amygdala, and hypothalamus. But when Bauby felt sad and produced tears, he could not cry. When he felt angry or fearful, he could hardly express this. Bauby could not gasp when shocked, laugh when amused, smile contentedly when seeing a loved one, or feel the release of sobbing when considering his fate. He was thus unable to match his "automatic" body—blood pressure, heart rate, vaso-motion—to his forebrain-generated feeling. Did this alter his emotional experience? We will never know, but it is a definite possibility.

In some curious fashion, Bauby's blunted body experience comes across in the emotional content of his book. In reminiscences about the past, he wrote, "My old life still burns within me but more and more of it is reduced to the ashes of memory." He narrates the day and immediate aftermath of his stroke with a palpable lack of immediacy in his emotional reactions. He reports that on his first trip back to Paris from the rehabilitation hospital in the south of France where he stayed, his "emotions got the better of me" but 4 months later, on another such trip, he "was unmoved by it." One feels more because of the facts of his case than because he writes of dismay and despair. In other words, we feel more as we—inevitably—place ourselves in Bauby's position than we do from the emotional content of his words. The idea that the sensory feelings of the body contribute to our full expression and experience of emotion is a concept that was promulgated by the great psychologist, William James, who wrote, "... we feel sorry because we cry, angry because we strike, afraid because we tremble... . Without the bodily states following on the perception, the latter would be purely cognitive in form, pale, colorless, destitute of emotional warmth." In the popular abbreviation of this idea, we see a bear, we run and therefore feel fear, rather than we see a bear, feel fear, and then run. Since Bauby was unable to move and had very little forebrain access to his autonomic system, his bodily sensations were reduced. We can postulate that as a result, his emotional experience was blunted.

THE LIMITATIONS EXPERIENCED BY CLIVE WEARING ARE DRAMATICALLY DIFFERENT FROM THOSE OF BAUBY

Let us contrast the life and limitations of Bauby with those of Clive Wearing, an accomplished music conductor, who suffered from encephalitis. After a long recovery from the acute illness, Wearing's ability to walk, conduct choral groups, read and play music, to breathe, listen to music, void, and stand up without feeling light-headed are unimpaired. Yet, he has one enduring and devastating deficit—memory. He has no ability to form new explicit memories. Every moment, he feels that he is awakening for the first time. Here is an example of the enormity of Wearing's deficit:

CW: Clive Wearing asks his wife, Deborah Wearing, "How long have I been ill?"

DW: Nine weeks.

CW: Nine weeks? I haven't heard anything, seen anything, touched anything, smelled anything. It's like being dead. What's it like being dead? Answer: Nobody knows. How long's it been?

DW: Nine weeks.

CW: Nine weeks? [He shakes his head] I haven't heard anything, seen anything, touched anything, smelled anything. It's like one long night lasting... how long?

DW: Nine weeks.

CW: Nine weeks?... One long night lasting... how long?

DW: Nine weeks.

CW: Nine weeks? I haven't heard anything, seen anything, touched anything, smelled anything. It's just like being dead. What's it like being dead? Answer: Nobody knows. How long's it been? I haven't heard anything, seen anything, felt anything, smelled anything, touched anything. It's been one long night lasting... how long?

The pathos of Wearing's condition is evident to us, and it is clearly evident to Wearing. When pressed to consider the inconsistencies in his belief of repeatedly waking anew—the fact that the diary is filled with entries, in his own handwriting, documenting previous awakenings—he rages. You can see this in numerous videos posted on YouTube. Wearing's life is devastated, and he knows it fully but only *implicitly*.

Clive Wearing's and Jean-Dominique Bauby's conditions are dramatically different and together encompass only the tiniest proportion of possible neural dysfunctions. The lesson to derive from their disparate stories is not a general principle about brain function or specific information about two vanishingly rare clinical conditions,

but rather the idea that *the impact of brain dysfunction is particularly poignant when it attacks our essence, who we are to ourselves*. People with cancer, heart disease, or diabetes may suffer both physically and psychologically with reduced quality-of-life and the knowledge of a fast-approaching end, but their sense of self does not change. After Bauby's brain stopped functioning correctly, he felt that he "faded away." When pressed to acknowledge that he has a problem with memory, Wearing asserts that he is missing consciousness, "I wasn't conscious, I have no knowledge of it at all! Consciousness has to involve ME!!" Wearing was devastated, unable to function, unable to think, unable to stitch together two moments in his life.

GO FORTH AND USE YOUR UNDERSTANDING OF NEUROBIOLOGY TO IMPROVE YOUR CHOSEN FIELD OF SPECIALTY

Although it is hard for the author to understand, the data suggest that at the very most, only about 10% of first-year medical schools will go into fields directly related to neurobiology—neurology, neurosurgery, and psychiatry. For the rest of you, beyond passing the boards, what are my hopes for what you will take away from this book?

First, I hope you see that neurobiology is all around you. When you go to the gym and watch your own and other's efforts to dissipate body heat—that is neurobiology. When you get up too fast in the middle of the night and feel light-headed, "go vagal"—that is neurobiology. When you deliberately look for a dim light in your peripheral visual field because you know that your fovea has no rods—that is neurobiology. When you watch a person over 45 read a restaurant menu at arm's length. Should you ever imbibe a substantial amount of liquor, move your head, and feel the room spin. When you watch a toddler on the move, practicing and practicing locomotion, all of that is neurobiology. When you are at the check-out counter at the grocery store and watch a clerk stop making change to answer a question—that is neurobiology.

This book has not covered every neural function that is important, interesting, or often negatively impacted by disease or trauma. Rather, my goal has been to give you a framework with which to understand nervous function. For instance, you learned how early visual experience is critical to the development of normal visual perception. This will be invaluable to those of you who become pediatricians and ophthalmologists as you see young patients with misaligned eyes.

It is also my hope that you have learned from this book a way to think of neural function and dysfunction and that this will translate into an ability to explain to patients in understandable terms the symptoms they are experiencing and the disease processes from which they suffer. There is not a single one of you who will not encounter at least one patient who presents with pain. Explaining to a patient how pain arises and your strategy for treating the pain will mitigate even a gloomy prognosis. People want to understand what is happening to their bodies. Explaining to a postmenopausal woman how a hot flash works and a few simple strategies to avoid

triggering them will make her feel better, even if hormone replacement therapy is contraindicated, and she understands that no other method exists for the prevention of hot flashes.

Beyond being doctors to your patients, you are individuals with friends and family, and in many cases, you may be the only doctor in your social group. I am the lone scientist among my family and friends of lawyers and artists, and I am called upon to explain all things neurobiological and most things medical. So, I imagine that for many of you, your family and friends will expect you to explain all things medical regardless of your future specialty. This is likely already happening, as the detail that you are still students is as ignored as is the detail that I am a Ph.D. rather than a M.D. Although very few of you will ever see a locked-in person or a case of global amnesia, I would venture to say that all of you will know, or already do know, someone who develops Parkinson's disease, multiple sclerosis, or has a stroke. You will also meet people with diseases that are not primarily neurological but which impact on nervous function: HIV disease, diabetes, and cancer patients on chemotherapy are obvious examples. Whether you encounter people with such diseases personally or in the clinic, you can help them by explaining their illness to them. Even a person with a devastating disease such as amyotrophic lateral sclerosis will feel relief at knowing and understanding that the symptoms he or she is experiencing are the expected ones—in essence, that he or she is not crazy. Such patients will want to know their prognosis, however dismal, because knowledge translates to a feeling of control.

Finally, I hope that you will use your knowledge of the power and potential of the nervous system to improve your chosen discipline, to further our understanding of a myriad of problems that have traditionally resided in non-neuronal specialties. Let me take a moment here to tell you a story. A patient comes in to a dermatologist with **alopecia**, meaning loss of hair all over her body. She also has reduced cortisol secretion. Two years later, she develops memory problems. A magnetic resonance image (MRI) reveals a gross enlargement of the temporal horn of the lateral ventricle, at the expense of the hippocampus. Another patient with the same three problems comes in. I am not sure when the physicians realized that the alopecia, hypocortisolemia, and amnesia stemmed from one disease process, but they did and published a report describing the two cases and postulating a pathophysiology of an autoimmune attack on a molecule common to hair follicles, corticotrophs, and hippocampus. Put yourself in their position. What would you do? Could you make the connections between dermatology, endocrinology, and neurology? Could you help the patient and deepen our understanding of biology at the same time?

There are also far more common problems to be solved. Individuals who suffer from schizophrenia smoke cigarettes. Does nicotine addiction hold a clue to the pathophysiology of this tragic and baffling disease? Can we stem the tide of myopia, already at epidemic proportions in many communities, and bound to get worse as children increasingly focus on hand-held devices? We know that women are flooded with oxytocin after giving birth, allowing them to nurse, and from animal experiments, we infer that this same hormone facilitates a new mother's bond with her child and family. Does this release fail in women who develop postpartum depression? Can we prevent the damaging effects of chronic activation of airway afferents while still enabling the acute protective functions? There are a myriad of such questions that are waiting for new, innovative thinkers.

I hope that those of you who go into sports medicine will think of motor units and cerebellar circuits and think up new, brain-friendly ways to improve upon the more traditional treatments of immobilization and rest to treat your patients. Today, in the early years of the 21st century, I find it remarkable that the most common effective “treatment” for incontinence is clothing, viz diapers. The potential of treating various types of incontinence with therapies directed at the central nervous system has hardly been tapped. The most common treatment for sleep apnea is a mask with positive pressure. Again, this is a peripheral, mechanical treatment that fails to utilize the power of the central nervous system. You can come up with better ideas.

Those of you, likely the majority, who will go into internal medicine or oncology, will see in great and tragic detail how mood and affect can impact outcome. Of two patients who come to you with similar physical findings, we know that the one who is happy and engaged in life will fare far better than the one who is depressed and unhappy. Why? Can we change this? These are important questions, and you can make a difference, you can make a connection, come up with an idea that links affect—generated by the brain—to the viscera that go awry in disease and after trauma.

So, I leave you with the message, “Go forth and be innovative.” The brain is spectacularly powerful—use yours for good.



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