CHAPTER THREE

THE MOST UNACCOUNTABLE OF MACHINERY

MY OWN BRAIN IS TO ME THE MOST UNACCOUNTABLE OF MACHINERY—ALWAYS BUZZING, HUMMING, SOARING ROARING DIVING, AND THEN BURIED IN MUD. AND WHY? WHAT'S THIS PASSION FOR?

—Virginia Woolf

Most of us are as mystified by our brains as Virginia Woolf, though perhaps less eloquent in our ignorance. Still, everyone has heard a few things about the wrinkled blob in the noggin—for instance, that we use only 10 percent of it. But who came up with this number? And why would we even have the rest if it weren't useful? Evolution doesn't usually make organs in such a way that they mostly go unused, just in case someone figures out one day what to do with the extra material. It's hard to imagine how 90 percent of the brain, lacking in value for most of us most of the time, could have ever come into existence. Researchers have been looking into what the brain does for many years now, and from what they have discovered, it doesn't seem that most of it is, in fact, resting idly.

People also tend to carry around with them one or both of two additional erroneous beliefs about the brain. The first is that functions of the brain, like perception, memory, or emotion, are located in specific areas. The other is that chemicals floating around in the brain determine our mental states. Unlike the 10 percent myth, these are actually part truths that, taken out of context, are patently false. We know, at least in a general sense, how the brain works, and it's not by islands of brain tissue or by isolated chemicals operat-

ing independently. Particular areas are important, but not on their own: they participate in functions by way of their synaptic connections with other areas. Chemicals are also important, but mainly because of their work at synapses within functional systems.

This chapter will give an account (albeit an abbreviated one) of this "most unaccountable of machinery," describing some basic facts that are necessary to understand the brain's synaptic systems. Although the discussion will have to get a bit technical along the way, this information is essential to my attempt to relate the self to synapses. Because I've kept things simple, those already in the know may wish to skip ahead. However, the novice will get a crash course on what neurons are, how synapses connect them together, and why synaptic connections are the key to brain function.

BRAINS: SO DIFFERENT, YET ALL THE SAME

We mammals belong to the group of animals called vertebrates, a subphylum we share with other backboned creatures, including birds, reptiles, amphibians, and fish. Mammals and birds separately descended from reptiles millions of years ago. In spite of this common ancestry, the brains of reptiles, birds, and mammals look very different. Beneath these dissimilarities, though, there's a common plan that's rigorously adhered to.

Every vertebrate brain can be divided into three broad zones: the hindbrain, midbrain, and forebrain. In the early years of the twentieth century, neuroscientists discovered that damage to each zone had a different predictable consequence.[1] For example, in studies of cats, it was found that purposeful, voluntary behavior and problem-solving ability were impaired when the forebrain was damaged. Nevertheless, even with massive injuries to the forebrain, some semblance of normal coordinated behavior remained. Such compromised animals could orient toward a noise or withdraw their paw from heat, and could walk, eat, and groom. They could even display full-blown emotional responses, especially those typically expressed in anger or fear, if the hypothalamus, a small region situated at the base of the forebrain, was spared. When larger lesions were made that removed all of the forebrain, including the hypothalamus, only rudimentary responses remained. These animals, when challenged with intense stimulation, could hiss, bare their teeth, unsheathe their claws, or swipe a paw, but could not manage to put all of these behaviors together into a coordinated defense or attack response. When the midbrain was damaged, the animal was essentially comatose—

alive physically, but not behaviorally or psychologically. And when the hindbrain was destroyed, life itself ceased.

From these crude experiments, it was concluded that the hindbrain controls very basic functions, those necessary for staying alive; the midbrain is involved in maintaining wakefulness and coarse, isolated behavioral reactions; and the forebrain coordinates complex behavioral and mental processes. It should not be surprising, given these effects of brain damage, that the forebrain (necessary for thinking and problem-solving) is the region that differs the most between mammals and other vertebrates and the hindbrain (necessary for life) the least. Nevertheless, all three levels are represented in all vertebrates, and even the evolutionarily advanced forebrain is structured according to a common underlying organizational plan that is applicable to every vertebrate species.

For example, the human forebrain consists of several subdivisions,[2] one of which is the wrinkled outer layer, the neocortex. This is the part of the forebrain that makes possible many of our higher mental functions. The designation *neo* reflects the fact that this brain region was, for many years, believed to be evolutionarily new, having emerged when mammals evolved from reptiles.[3] Other vertebrates were thought to have a primordial or older cortex but not a mammalian or neocortex. This view began to change, though, in the late 1960s and early 1970s, when new techniques for studying the brain became available.[4] Based on the patterns of chemical staining and nerve connections discovered with these techniques, the organization of the brain came to be better appreciated, and researchers were able to use this information to find the equivalent (or at least the semblance) of a neocortex in both birds and reptiles, suggesting both that it wasn't so new after all and that it certainly wasn't unique to mammals. The reason this cortex had not been found in these animals earlier was because of its unusual location, buried beneath other brain areas, instead of resting on top, as it does in mammals.

While at the level of overall brain structure a similar organizational plan applies to many different animals, it is not the case that all brains are the same. A given brain area can vary enormously in size and complexity between different species, allowing some animals to do things that others cannot. In amphibians, for example, an area in the midbrain called the tectum is especially well developed, making it possible for most frogs to thrust their tongue into the flight path of an insect and capture it,[5] a feat most people can't accomplish. Bats and rats can hear things that we cannot, and bees use a magnetic sense, which we do not have, to guide their movements.[6] Different

species have been subjected to different evolutionary pressures, and their brains reflect their unique histories.[7]

The most obvious difference between the mammalian and other vertebrate brains is the extent to which the cortex has expanded. Although, as we have seen, reptiles and birds are now known to have some neocortex, the mammalian neocortex is far more elaborate than the equivalent areas in these other species.[8] And within mammals, there are distinctions as well: the neocortex is bigger and more differentiated in primates than in rodents, and in humans more so than in monkeys. These changes in cortical size and complexity are, however, superimposed on a basic neocortical plan. For example, in all mammals, processes related to sensation (vision, audition, touch) are represented in the rear and processes involved in controlling movement in the front of the cortex.

Within a given species, the similarities of cortical organization are striking. Early anatomists discovered that the major patterns of cortical wrinkles, which appear to be randomly arranged to the uninitiated eye, are amazingly consistent from person to person, and can be used as landmarks to identify various regions of the neocortex.[9] What's remarkable is that these purely structural parcels, defined by the wrinkles, turn out to correspond to functional divisions, areas that participate (by way of their synaptic connections with other cortical and/or subcortical areas) in different aspects of mental life and behavior.[10] For example, the area of the cortex involved in controlling precise movements of various body parts is located just in front of the central sulcus, one of the major wrinkles in the cortex, while touch, hearing, and visual areas are defined by their own wrinkles, as are areas involved in language comprehension and speaking. On careful examination, some variation in the organization of cortical or other brain areas is evident in different people, but the basic overall architectural plan of the brain is pretty much the same in any two individuals.

In spite of the tremendous similarity of our brains, we all act differently, have unique abilities, and have distinct preferences, desires, hopes, dreams, and fears. The key to individuality, therefore, is not to be found in the overall organization of the brain, but rather in the fine-tuning of the underlying networks. To understand the defining qualities of each person, we need to go beyond the superficial organization of the brain (its division into broad regions and areas within these) and turn to the microscopic structure and function of neural systems, and especially to the cells and synapses that constitute them.

THE CELL WAR

All organs and tissues of the body are composed of cells. But unlike the cells in other body parts, brain cells, or neurons, directly communicate with one another. There's nothing magical about the process—neurons are simply built in a way that allows them to exchange information with one another in ways that other cells cannot.[11] Common patterns of communication between neurons ensure that all human brains work in basically the same way, whereas subtle differences in these patterns of communication give rise to the distinctive qualities that we each have.

The existence of cells in the brain and other parts of the body is taken for granted today, but this knowledge was only made possible by the further development of the microscope in the nineteenth century. Around 1837, Matthias Schleiden, a German botanist, first proposed that plants were made up of discrete units, or cells. The following year, his friend Theodor Schwann extended the notion to animals, and thereby brought botany and zoology together in a single theory, the so-called cell theory,[12] which argued that all living things are composed of cells.

Whether cell theory was applicable to the brain was a topic that was fiercely debated for decades. When early brain anatomists examined brain tissue under a microscope, they did see structures resembling cells. But unlike cells in other organs, brain cells had fine fibers extending out of them (fig. 3.1). Some scientists concluded that this meant that the brain was unique—not composed of discrete cells but instead made up of an entangled mesh or reticulum of continuously connected elements. Others, though, argued that the fundamentals of cell theory applied equally to the brain.

Two of the major figures in the debate were Santiago Ramón y Cajal of Spain and the Italian anatomist Camillo Golgi.[13] Golgi, working in his kitchen, invented methods for staining the brain that allowed better visualization of its microscopic anatomy. He favored the reticular theory. Ironically, on the basis of the methods pioneered by Golgi, Cajal argued forcefully for the application of the cell theory to the brain, and won many converts. One of these was Wilhelm Waldeyer, who in 1891 published a paper in which he suggested that brain cells be called neurons. In this paper, he also coined the phrase *the neuron doctrine* to account for the application of the cell theory to the brain. Cajal apparently considered the doctrine his, at least in spirit if not name, and was not happy to have had his thunder stolen by Waldeyer.[14] But the loss in stature, if any, was temporary. Every graduate student in

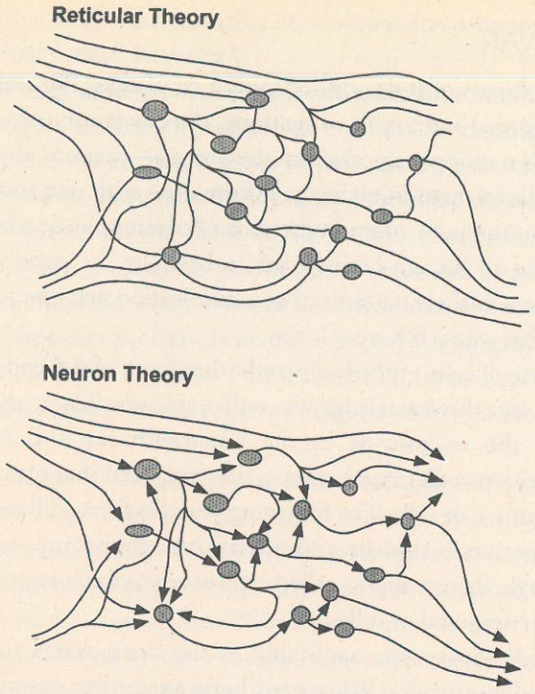

FIGURE 3.1 RETICULAR VERSUS NEURON THEORY

In the late nineteenth century, scientists fiercely debated the question of whether the brain was made up of a reticulum of continuously connected elements or, instead, of individual cells, neurons, that communicated with one another. By the beginning of the twentieth century, the so-called neuron doctrine had emerged as the prevailing view.

neuroscience today knows who Cajal was, whereas few have ever heard of Waldeyer.

One of the early and largely unrecognized soldiers in the neuron war was the young Sigmund Freud. After completing his medical training in Vienna, Freud accepted a position as a famulus, or research scholar, and studied the nervous system of fish and crayfish.[15] As early as 1883, long before the neuron doctrine was codified, he promoted the idea that nerve cells are physically separated from one another.[16] This concept later figured prominently in one of his earliest forays into psychological theory. In *Project for a Scientific Psychology,* written in 1895 but unpublished for many decades,[17] Freud stated that "the nervous system consists of distinct and similarly constructed neurones . . . which terminate upon one another." He introduced the term *contact barriers* to describe the points where neurons abut, and suggested that interactions between neurons across contact barriers make possible memory, consciousness, and other facets of the mind. Although these notions were amazingly sophisticated for their time, Freud felt that progress in understanding the brain would be too slow for his taste and so abandoned a neural theory of the mind in favor of a purely psychological one.[18] The rest is history.

Two years after Freud wrote his *Project,* Sir Charles Sherrington proposed a different term for the connections between neurons.[19] Sherrington had been working on the reflex problem.[20] A reflex is the simplest kind of neural circuit that controls behavior. When your physician taps you on the knee, your leg jerks because the tap elicits sensations that are transmitted along *sensory* nerves that originate in your knee and travel to your spinal cord. The messages in the sensory nerves trigger activity in *motor* nerves that come out of the spinal cord and end in your leg muscles, leading to the jerk. Sherrington realized that the gap between the sensory and motor neurons had to be bridged somehow if information carried by the sensory nerves was to be transferred to the motor nerves. He was probably unaware of Freud's contact barriers, and chose to call the gaps synapses, derived from the Greek word meaning to clasp, connect, or join.[21] The notion of synapses as points of communication between cells is one to which we still adhere, and which is essential to our efforts to understand who we are in terms of brain mechanisms.

In 1906, Cajal and Golgi shared the Nobel Prize for their groundbreaking research on brain anatomy. Although the neuron doctrine had gained considerable support by then, Golgi clung bitterly to the reticular theory at the award ceremony.[22] Still, definitive proof that the nervous system is composed of cells did not come until many years later. With the invention of the electron microscope in the 1950s, scientists could finally examine the brain in sufficient resolution to see that the tiny fibers extending out of a neuron do not typically make direct physical contact with neighboring cells.[23] Indeed, they are separated by tiny spaces, synaptic spaces, across which the brain does its business.

WHAT MAKES NEURONS SPECIAL?

By knowing the function performed by a few cells of most organs in the body, whether the liver, kidney, or gall bladder, you can deduce the organ's overall function.[24] This is not true of the brain, however, where cells participate in myriad activities, from seeing and hearing to thinking and feeling, from awareness of self to the incomprehension of infinity. The architecture of a

neuron helps us begin to understand why the brain is so multifunctional, while organs like the pancreas and spleen are not.

Neurons have two major parts. The first is the cell body (fig. 3.2), which is involved in important housekeeping functions, such as storing genetic material and making proteins and other molecules that are necessary for the cell's survival. The cell body does much the same work in neurons as it does in other cells. The major structural difference between neurons and other cells lies in the special appendages that neurons have—the nerves. These fibers, which extend out of the cell body, are what caused all the confusion in the nineteenth century about whether the brain was, like other organs, composed of discrete cells.

Nerve fibers are sort of like telephone wires. They allow neurons in one part of the brain to communicate with neurons in another. By way of these connections, communities of cells that work together to achieve a particular goal can be formed across space and time in the brain. This capacity underlies all of the brain's activities and is absent in other organs.

There are two varieties of nerve fibers, axons and dendrites (fig. 3.2). Axons are output channels, and dendrites are input channels. An axon carries messages to other cells. It can end nearby, allowing communication with its close neuronal neighbors, or it can stretch over very long distances, as much as several feet. If you are standing still and decide to take a step, the movement of your leg on the basis of your decision involves axons that originate in cell bodies located in the movement control regions in the frontal cortex (just behind your forehead) and that travel uninterrupted to the base of the spinal column (in the region of your lower back).

The end of the axon, called the terminal, is the point at which the sending neuron communicates with receiving neurons. Although terminals most often form connections with dendrites, they can also contact cell bodies or other axons.[25] Dendrites, too, sometimes communicate between one another.[26] In order for the long axons descending from your frontal cortex to your spinal cord to cause your leg to move, the terminal has to contact dendrites of the receiving cells in the spinal cord. The axons of these receiving cells then extend out and terminate at muscles in your leg. The arrival of signals at the muscle leads to contraction, and thus movement.[27]

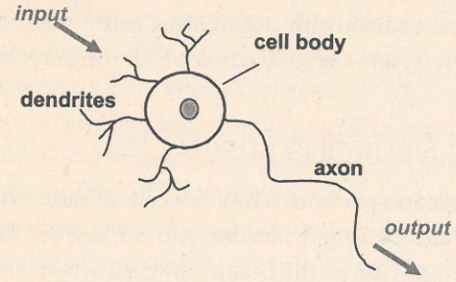

FIGURE 3.2 COMPONENTS OF A NEURON

All neurons contain three basic parts: a cell body and fibrous appendages called dendrites and axons.

Many dendrites have little knobs called spines extending from them (fig. 3.3). These are readily seen when brain tissue is stained with the methods

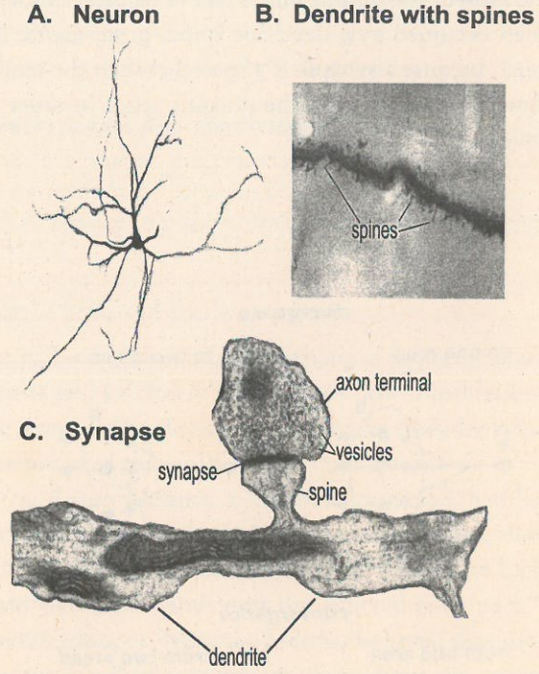

FIGURE 3.3 WHAT A NEURON LOOKS LIKE

Upper left: A single neuron and many of its dendrites. This neuron had been filled with a dye so that its shape can be seen. *Upper right:* A high magnification of a small piece of a dendrite showing the protrusion of the small spines from the dendritic shaft. Spines are often where axons from other neurons terminate and form synapses. *Bottom:* A highly magnified electron-microscopic picture of an axon terminal with vesicles forming a synapse with the spine of a dendrite. When an electrical charge travels down the axon to the terminal, neurotransmitter is released from the vesicles and drifts across the small synaptic space between the terminal and the spine. The neurotransmitter then binds to receptors on the spine and initiates electrical events in the receiving neuron.

developed by Golgi. Spines are especially important as receivers of messages from axons, and play a key role in brain development, as well as in learning and memory, as we will see later.

Most neurons have only one axon. However, each axon branches many times before it ends, allowing a single neuron to spawn many terminals. The result is that the messages sent out from one cell can affect many others. This is called divergence (fig. 3.4). At the same time, each neuron can receive inputs from numerous others. This is called convergence (fig. 3.4).

The point at which the sending and receiving elements of neurons meet is our star, the synapse. Because information usually flows across the synapse starting from the axon terminal, this side is said to be presynaptic, and the receiving side, often occupied by a dendritic spine, postsynaptic (fig. 3.5). As Sherrington noted, because a synapse is a space between the sending and receiving cells, something has to cross the synaptic space in order for the two cells to communicate.

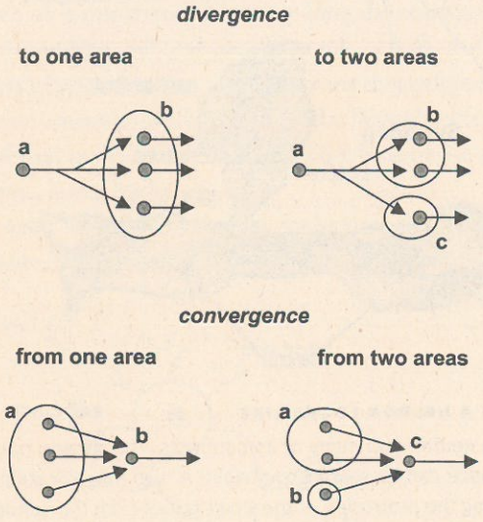

FIGURE 3.4 DIVERGENCE AND CONVERGENCE

Divergence exists when a neuron gives rise to axons that branch and terminate on multiple targets, whereas convergence exists when a single neuron receives inputs from multiple sources.

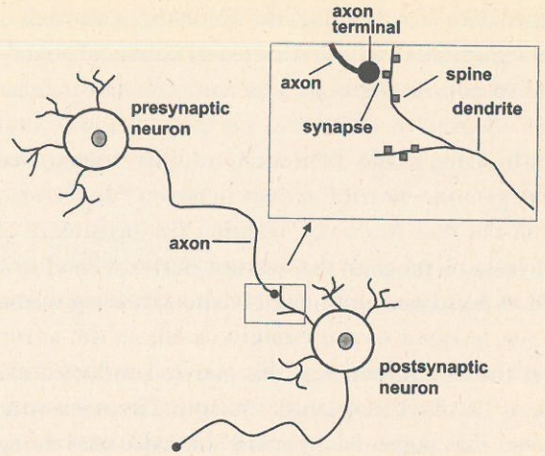

FIGURE 3.5 PRESYNAPTIC AND POSTSYNAPTIC NEURONS

This figure shows two neurons, one presynaptic to the other. The axon of the presynaptic neuron terminates at the dendrites of the postsynaptic neuron. Often, such terminations form synapses on the spines (small protrusions) on dendrites.

GALVANIZED FROG LEGS

The question of how information is exchanged between neurons across the synaptic space is tied in closely with that of how information is transferred along a nerve fiber of a single neuron. Before we consider synaptic transmission, we therefore need to consider nerve conduction.

In the 1770s, Anton Mesmer, a Viennese physician, had been using iron magnets to treat a variety of physical and mental maladies, until he found he could have the same effect without the magnets when he looked into a patient's eyes and waved his hands over the afflicted body part.[28] This was the birth of mesmerization, or hypnosis. Mesmer believed that some mysterious, magnetically sensitive fluid was present throughout the universe, including the human body, and that he could help his patients by using his own animal magnetism to alter this fluid.[29] At the time, little was known about the physiology of the nervous system, and any theory, including one as wacky as animal magnetism, seemed possible.

A few years later, the Italian Luigi Galvani noticed that the amputated leg of a frog hung from an iron trellis with a brass hook twitched during a lightning storm.[30] He also found he could make a frog leg kick at any time he wished if he touched the nerves within the wound with one metal and the

foot with another. This was, in effect, the first battery. Galvani, in the tradition of Mesmer, concluded that the metals were conducting vital spirits from the frog. So-called animal electricity was an occult rather than a scientific phenomenon.[31]

Several decades later, Carlo Matteucci, another Italian, made the first measurements of genuine electrical activity in nerves.[32] In Germany, Johannes Müller and Emil Du Bois-Reymond, realizing the importance of this observation, began a research program that rescued electrical conduction in nerves from the world of mysticism and turned it into a thriving scientific research field.[33]

At the time, the assumption was that nerves conducted electricity like wires. But one of Du Bois-Reymond's students, Hermann von Helmholtz, did an experiment that suggested otherwise. He calculated the speed of electrical conduction in frog nerve fibers by measuring how much time elapsed before a given muscle twitched when nerves of different lengths were electrically stimulated. Although conduction time was fast—about 40 meters per second (roughly 40 mph)[34]—it wasn't as fast as electricity, which can under certain conditions flow through a wire at about the speed of light.

From these simple but informative experiments, it became clear that nerves do conduct electricity, but in a special way. Electricity does not flow passively through a nerve as it does through a wire. Rather, impulses conducted through nerves are *biologically* propagated, moved along by electrochemical reactions, a process that takes a lot longer than passive physical conduction.

The biologically propagated impulse in a nerve is called an action potential. This dramatic electrical event is normally initiated at the point where the axon emerges from the cell body. Once triggered, it travels like a rolling wave down the axon toward the terminal. The propagation occurs as a kind of neurodomino effect—an electrical change in one part of the axon membrane produces a similar change in adjacent parts, and so on, all the way down to the terminal. Action potentials can be triggered artificially by electrical stimulation, which makes them easy to study, but normally they occur in a cell when orders come from synaptic inputs.

Work by many pioneering neuroscientists established the basic principles of electrical propagation in axons, which became the foundation for much of what we now know about the working of neurons. A good deal of this research was performed using the giant axons of squids, the sheer size of which made it easier to investigate electrical conduction. Especially noteworthy were the studies performed in the 1940s by Alan Hodgkin and Andrew Huxley in England. Building on Ohm's law of electricity (which states that voltage is equal to current times resistance), they characterized in precise mathematical form the basic features of electrical transmission in axons. The Hodgkin-Huxley equations are still used today to calculate current, voltage, and resistance in axons.

SYNAPTIC CHATTER

The existence of electrical conduction in nerves suggested to late-nineteenth-century scientists that electrical impulses played a critical role in the normal functions performed by the brain. A key related question was whether electrical propagation was sufficient to explain how the brain worked. Sherrington's studies of reflexes determined that it was not.

Electrical impulses in sensory and motor nerves clearly seemed involved in reflexes: when sensory nerves detect a tap on your knee, they conduct electrical impulses that, in turn, lead to electrical impulses in motor nerves, and to the jerk. But how does the sensory nerve communicate with the motor neuron? Sherrington demonstrated that while electrical stimulation of a sensory nerve elicited an electrical response in the motor nerve, stimulation in the motor nerve did not evoke a response in the sensory nerve (fig. 3.6). He concluded that the junction between cells, the synapse, had a valvelike property—it only transmitted in one direction, from sensory to motor nerves.[35] This was particularly significant ammunition against the reticular theory, for if neurons were continuously connected and communicated only by electrical conduction, then motor nerves should have as sizable an effect on sensory nerves as the other way around. Neurons must therefore communicate with one another by some means other than mere electrical conduction.

Subsequent research revealed that the one-way conduction between neurons is due to the fact that synaptic transmission involves the release of chemicals from storage sites in the presynaptic axon terminal. These molecules are released when action potentials propagated from the cell body reach the terminal. The released chemicals then drift across the liquid-filled synaptic space[36] and come in contact with spines or other portions of the postsynaptic cell. Because the chemical storage sites usually are present in the presynaptic terminal and not in the postsynaptic dendrite, transmission only occurs in one direction. These chemicals are called neurotransmitters, since they allow neurons to communicate across the synaptic gap—they transmit between neurons.

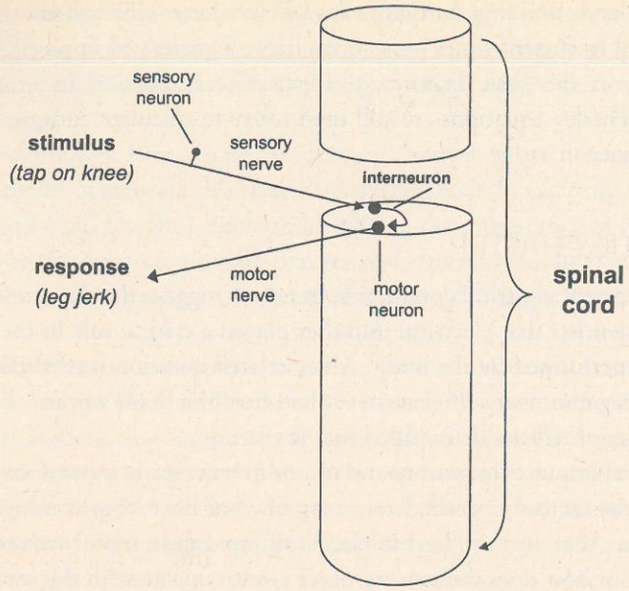

FIGURE 3.6 A SPINAL REFLEX

The basic elements of a spinal reflex include sensory neurons that receive messages about an external stimulus, motor neurons that initiate muscle movements, and interneurons in the spinal cord that link the sensory and motor neurons. Sherrington's studies of spinal reflexes led him to the conclusion that synaptic transmission is a one-way street.

The chemical nature of neuronal transmission was suspected from studies in the early 1900s showing that the effects of electrical stimulation of nerves could be mimicked or blocked by certain chemical agents. But it was an ingenious experiment by Otto Loewi in the 1920s that provided the ultimate proof.[37] He removed the hearts from two frogs, leaving the nerves connected to one heart but not the other, and infused each with a saltwater solution (similar to normal body fluid). He then electrically stimulated the nerves on one, which changed the beat rate of the heart (the heart is postsynaptic to these nerves). When he removed the solution from the stimulated heart and injected it into the other, the heartbeat changed in the unstimulated heart, much as if it had been stimulated, indicating that some chemical that had been released in the stimulated heart was transferred in the solution to the other.

While Loewi's experiments involved the connection between a nerve and a

muscle—the heart, in this case—essentially the same thing happens when the connection is between two neurons. That is, the arrival of the action potential in the presynaptic terminal leads to the release of neurotransmitter into the synaptic space.

The release of neurotransmitter molecules from the presynaptic terminal is a means, not an end. Its goal is to generate an electrical response in the postsynaptic cell. Although it is often the dendrites that are the postsynaptic beneficiaries of the chemical message, the electrical change produced in the dendrite has to be propagated to the cell body, and then to the axon, before an action potential can occur. This is so because the action potential is generated in the initial part of the axon where it connects with the cell body (fig. 3.7).

The arrival of transmitter from a single presynaptic terminal is typically not sufficient to produce an action potential in the postsynaptic cell (fig. 3.7). Only if the postsynaptic cell is bombarded with transmitter molecules from many presynaptic terminals at about the same time—within milliseconds—will an action potential result.[38]

A given postsynaptic cell is believed to receive relatively few synaptic contacts from any one presynaptic neuron. As a result, much of the convergence that drives a postsynaptic cell toward action potentials comes from the convergence of different presynaptic cells onto the postsynaptic neuron (that is, the near-simultaneous arrival of neurotransmitter from different presynaptic neurons). In order for the inputs to arrive in the postsynaptic cell body at about the same time, action potentials have to have been triggered in the various presynaptic cells at about the same time. The timing has to be adjusted for different lengths of axons, since, as Helmholtz demonstrated, the longer the axon, the longer it takes for the action potential to travel down it. Keeping time in the nervous system is a very complex job.

Once the postsynaptic cell generates an action potential, its role shifts from that of a receiver to a sender. It now becomes a presynaptic neuron that helps fire action potentials in other cells.

The full sequence of communication between neurons is thus usually electrical-chemical-electrical: *electrical* signals coming down axons get converted into *chemical* messages that help trigger *electrical* signals in the next cell. There are also synapses through which communication between presynaptic and postsynaptic sites is purely electrical,[39] but chemical transmission is the more prevalent form. Thus, much of what the brain does involves electrical-to-chemical-to-electrical coding of experience. As hard as it may be to imag-

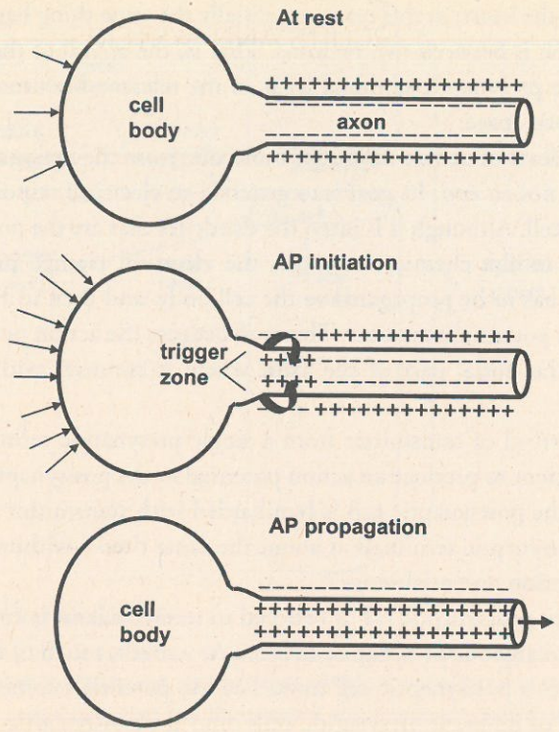

FIGURE 3.7 ACTION POTENTIALS

When a neuron is activated by other neurons, an action potential is initiated. This electrical storm begins at the trigger zone (the region where the axon joins with the cell body) and travels down the axon. *Top:* Neurons are "at rest" when they are not receiving sufficient inputs to alter their electrical properties. When at rest, the electrical charge of the inside of the axon is negative with respect to the outside (see the + and − signs along the axon). *Middle and bottom:* When enough inputs (arrows on left) converge at about the same time, an action potential is generated and propagated down the axon toward the terminal. The propagation process involves a wave of electrical change (inside becomes more positive at that spot) that moves step-by-step down the axon. When the terminal is reached, neurotransmitter is released into the synapse. Based on figure 2.6 in Guyton 1972.

ine, electrochemical conversations between neurons make possible all of the wondrous (and sometimes dreadful) accomplishments of human minds. Your very understanding that the brain works this way is itself an electrochemical event.

FROM CELLS TO CIRCUITS AND SYSTEMS

Every human brain has billions of neurons that together make trillions of synaptic connections among one another. Chemicals are oozing and sparks flying constantly, during wakefulness and during sleep, during thoughtfulness and during boredom. At any one moment, billions of synapses are active.

Imagine a large cocktail party at which hundreds of people are standing around and chatting with one another. If you were to place a microphone in the chandelier at the center of the room high above the crowd, you probably wouldn't be able to make out what was being said, for the many unrelated conversations would blend together in the microphone. You'd learn more by listening in on small groups than by eavesdropping on the whole room at once. In the same vein, it's not particularly instructive to ask what all of the brain's billions of neurons and trillions of connections are up to collectively at any one time. Different groupings of cells are doing different things, so attempting to take a reading of them all together doesn't tell you much. It would be more informative to examine the operation of specific circuits or systems.

A *circuit* is a group of neurons that are linked together by synaptic connections. A *system* is a complex circuit that performs some specific function, like seeing or hearing, or detecting and responding to danger. Seeing, for example, involves the detection of light by circuits in the retina, which sends signals, by way of the optic nerve, to the visual thalamus, where the visual information is processed by circuits that relay their output to the visual cortex, where additional circuits engage in further processing, ultimately creating visual perceptions. The visual system, like other brain systems, can thus be thought of as a series of hierarchically arranged circuits linked together by synaptic connections to perform some function.

Synaptic interactions between two types of neurons, called projection neurons and interneurons, are key to understanding how circuits and systems function.[40] Projection neurons have relatively long axons that extend out of the area in which their cell bodies are located. In a hierarchical circuit, their main job is to turn on the next projection cell in the hierarchy (fig. 3.8). They do this by releasing a chemical transmitter that increases the likelihood that the postsynaptic cell, the next projection cell, will fire its own action potential. Projection cells tend to activate or excite postsynaptic cells.

Interneurons, also called local circuit cells, send their short axons to nearby neurons, often projection neurons, and are involved in information processing within a given level of a hierarchical circuit (fig. 3.8). One of their main

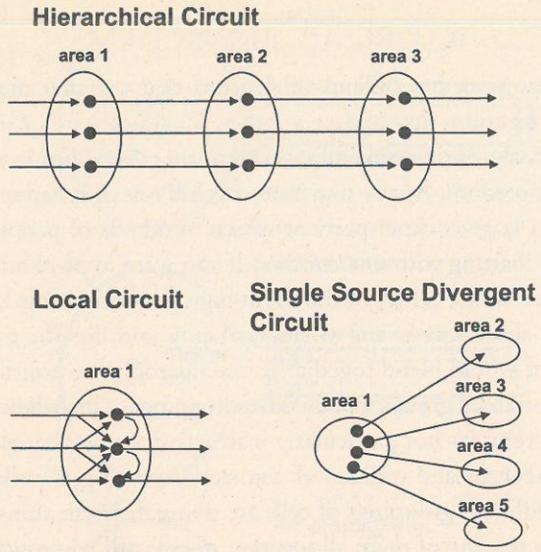

FIGURE 3.8 THREE TYPES OF CIRCUITS

Information is transmitted from area to area in sequence in hierarchical circuits. At each level of the hierarchy, though, processing is regulated by other kinds of circuits. Local circuit connections alter the processing at each hierarchical stage and also determine the ease with which activity in one area can influence the next. Single source divergent projections are typically made up of neurons located in one brain region that possess a particular chemical (typically, a neuromodulator like serotonin or dopamine—see text). These chemicals are then released at widespread areas and can influence processing by other circuits. Transfer of information from one level of a hierarchical circuit to another typically involves excitatory connections that are regulated by inhibitory local circuits, and both hierarchical and local circuit transmission is modulated by single source divergent connections. The terminology for these three circuit types is based on Bloom and Lazerson 1985.

jobs is to regulate the flow of synaptic traffic by controlling the activity of projection neurons. Inhibitory interneurons release a transmitter from their terminals that decreases the likelihood that the postsynaptic cell will fire an action potential. These neurons play an important role in counterbalancing the excitatory activity of projection cells.

Projection cells tend to be idle in the absence of inputs from other projection cells. Inhibitory interneurons, though, are often tonically active, which means they are firing all the time. Part of the reason why projection cells are inactive when not being stimulated is that they receive tonic inhibition from

interneurons. As a result, when excitatory inputs try to turn on a projection cell, preexisting inhibition of the projection cell has to be overcome. The balance between excitatory and inhibitory inputs to a neuron determines whether it will fire.

The amount of inhibition affecting a cell can change from moment to moment, depending on other factors. For example, when projection cells in one area of a hierarchical circuit send enough convergent inputs at about the same time to activate projection cells in the next area, the level of inhibition in the second area usually goes up as well. This happens because the excitatory inputs to an area often activate interneurons as well as projection neurons. The momentary increase in excitatory inputs to interneurons leads to a momentary increase in their inhibitory behavior, which in turn produces a momentary inhibition of the projection neurons. So-called elicited inhibition contrasts with tonic inhibition. Because rapidly changing states of excitation and inhibition direct the flow of traffic through the brain, it's easy to understand how a breakdown in the flow of impulses could lead to neural gridlock.

Consider an example that will help illustrate how elicited and tonic inhibition regulate excitation. Imagine a circuit consisting of two projection neurons (A and B) linked together in a series (fig. 3.9). When A is active, B fires. If the job of the circuit were to make B fire action potentials as often as possible as long as A is active, these two neurons would be sufficient to do the job. But suppose its job instead is to take a barrage of action potentials in A and turn them into fewer action potentials in B, something that actually occurs quite often in the brain. This could be achieved by giving neuron B an inhibitory playmate (I). This local circuit neuron, like B, receives the output of A and then connects with B. So when A fires, it turns on B and I, and each produces an output. The output of B helps turn on the next cell in the circuit, while the output of I turns B off. As a result, B now produces fewer action potentials when it is fired by A.

Now suppose that the interneuron I is constantly inhibiting the projection cell B. With this tonic inhibition added in, it is going to be much harder for the input from A to trigger the projection cell. If we put more excitatory neurons in with A to drive B, and time arrival just so, the tonic inhibition can be overcome. The cell can now be continuously activated. But being stuck in fast-forward is not good for neurons, which can be damaged or even destroyed by unchecked excitation. Each burst of excitation thus needs to be countered with another round of inhibition. That's where elicited inhibition, like that described above, comes in. When an excitatory surge overcomes

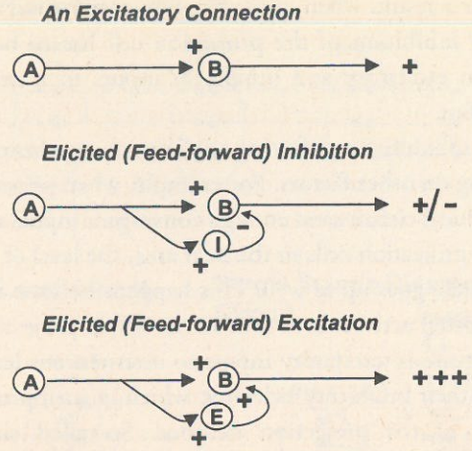

FIGURE 3.9 EXCITATION AND INHIBITION IN CIRCUITS

Excitation and inhibition are illustrated by way of an excitatory connection from A to B that is regulated by the inhibitory connection from I to B. The + and − signs to the right indicate the effect of the particular combination of connections. *Excitatory connection:* Activity in A leads to activity in B (+ on the right). *Feed-forward inhibition:* Activity in A leads to activity in B. A also activates I, which in turn inhibits B. B is thus first turned on by A (+ on right) but then turned off by I (− on right). The excitation of I by A thus gates or regulates the excitation of B by A. *Feed-forward excitation:* Activity in A leads to activity in B. Also activates E, which in turn further excites B. The excitation of B by A is thus amplified by E (+ + + on right).

tonic inhibition, elicited inhibition can rein in the excitation, resetting the circuit, preparing it for new inputs. There are many variations on this theme of tonic and elicited inhibition, but the scenario just described gives an idea of how inhibition in general works.

Inhibition is a very useful device in neural circuits. It adds tremendously to the specificity of information processing, filtering out random excitatory inputs, preventing them from triggering activity. Only if the excitatory inputs arrive simultaneously can they overcome the inhibition and elicit activity. And once activity is elicited, inhibition is important for keeping the excitation in check and resetting the circuit.

Although many local circuit cells are inhibitory, some are excitatory. Just as inhibitory interneurons can be thought of as filters, excitatory interneurons can be viewed as amplifiers. Again imagine a circuit consisting of neurons A and B connected in series. As before, B is associated with an interneuron, but in this case it's an excitatory interneuron (E), and the axon of A branches and contacts both B and E (fig. 3.9). When A turns on B, the interneuron E is also activated, and its output causes further excitation of B. As a result, the output of B is amplified by an excitatory interneuron just as it was reduced by the inhibitory interneuron. But, as we've seen, all this excitation ultimately has to be regulated, both to maintain normal functions and to prevent injury.

THE CHEMICAL BROTHERS

The job of a projection neuron, as we now know, is to turn on the next projection cell in the circuit. This means that action potentials in the axons of projection cells have to trigger the release of chemicals that cross the synapse and contribute to the firing of an action potential in the postsynaptic cell. Projection cells thus need to use a chemical neurotransmitter that has two properties. The transmitter first must be able to act quickly at postsynaptic sites—otherwise, our perceptions and other mental states could not keep up with rapidly changing events. And it must also be able to change the electrical state of the postsynaptic cell in such a way that the occurrence of an action potential is more likely to occur. Both requirements (speed and excitation) are fulfilled by the amino acid neurotransmitter glutamate, which is the main transmitter in projection neurons throughout the brain.

Glutamate actually has two roles in body function. In addition to serving as a neurotransmitter in the brain, it also plays a major part in basic life-sustaining metabolic processes that go on continuously throughout the body. For example, it is a building block in the construction of peptides and proteins, which are basic ingredients of living tissues. And, in the brain, it helps detoxify ammonia, which is a natural by-product of certain chemical reactions. Although glutamate is now known to be a ubiquitous excitatory transmitter in the brain, its role in transmission was for a long time hard to dissociate from its so-called metabolic functions.[41]

In contrast, inhibitory neurons, especially inhibitory interneurons, often release the amino acid GABA (short for gamma-aminobutyric acid) from the terminals of their short axons.[42] In contrast to glutamate, this inhibitory transmitter reduces the likelihood of an action potential being generated in the postsynaptic cell. By sending axons to nearby projection neurons, GABA interneurons thereby regulate the flow of traffic through a given area.

GABA actually was identified as a neurotransmitter long before glutamate.

Because it was well established that glutamate was one of the essential chemical components involved in the synthesis of GABA, its metabolic role in GABA production hampered the discovery that glutamate was itself a neurotransmitter.

Glutamate and GABA are together responsible for much of the neurotransmission business in the brain. If you understand the work done by these two chemicals, you will understand quite a lot about how synapses function. These and all other transmitters work by attaching to molecules called receptors on the postsynaptic cell. Receptors selectively recognize and bind (literally, hold on to) transmitter molecules. Glutamate receptors recognize and bind glutamate, but ignore GABA (fig. 3.10); GABA receptors are just as selective (fig. 3.10). How, then, does the binding of glutamate and GABA molecules to their receptor molecules lead to excitation and inhibition?

All cells in the body are completely enclosed by a membrane, which defines the boundary of an individual cell. The membrane is like a formfitting bag, a spandex suit, in which the cell is contained. In neurons, it covers the axons and dendrites as well as the cell body. The space outside the membrane between neurons is called the extracellular space. The fact that the extracellular space is filled with liquid has two important consequences.

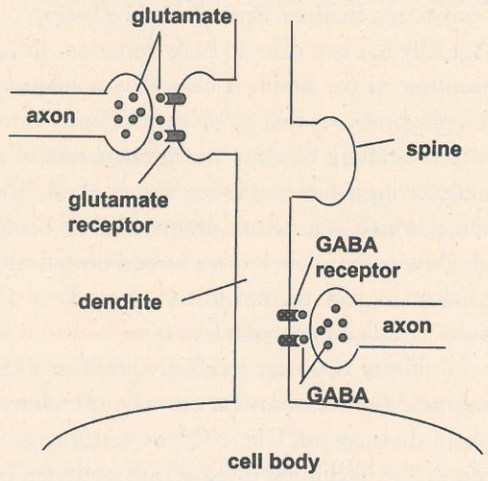

FIGURE 3.10 GLUTAMATE AND GABA SYNAPSES

The two major neurotransmitters are glutamate and GABA. These are released from different presynaptic neurons and bind to distinct postsynaptic receptors.

First of all, this liquid is a medium that allows transmitter molecules to cross the extracellular space between presynaptic and postsynaptic sites—the synapse. Transmitters do this by diffusing out from the terminal. The distance they have to travel is very small (it's measured in tiny units called angstroms, one of which equals one ten-millionth of a millimeter), making the postsynaptic site a close and easy target.

The second point is that extracellular liquid contains all sorts of chemicals, many with electric charges, that influence cellular function. The cell membrane keeps chemicals that are inside and outside the cell separate. At rest (when the cell is not being influenced by inputs), the chemical composition of the inside of the cell is more negatively charged than the fluid outside, due to the kinds of ions that are present on the other side of the cell membrane. Neuroscientists have measured the difference in electrical charge between the inside and outside of a nerve cell. In general, the inside of a neuron that is not being stimulated is about 60 millivolts (60 one-thousandths of a volt) more negative than the outside. In other words, the resting potential of the cell is about −60 mV.

For our purposes, the actual voltage is not that important. All we need to keep in mind is the fact that the membrane potential is fairly negative at rest. When a neuron is stimulated by excitatory inputs from other neurons, however, the membrane potential becomes more positive (see fig. 3.7). The reason for this is related to the way that glutamate works as a neurotransmitter.

Glutamate receptor molecules span the cell membrane, with part facing inside the cell and part facing outside. When glutamate (released from a presynaptic terminal) binds to the outside part of a postsynaptic receptor, a passage opens up through the receptor, allowing positively charged ions in the extracellular fluid to move inside the cell, which changes the chemical balance between outside and inside. If enough glutamate receptors are occupied on the postsynaptic cell at about the same time, and the voltage inside becomes sufficiently positive, then an action potential occurs.

In contrast, when GABA receptors are occupied, the inside of the cell becomes more negative (due to the influx of negative ions, especially chloride, through a passage in the GABA receptor). This makes it harder for glutamate released from other terminals to change the concentration of the positive ions in the postsynaptic cell sufficiently to trigger an action potential. Whether an action potential occurs, then, depends on the relation between glutamate (excitation) and GABA (inhibition). And since any one cell receives many excitatory and inhibitory inputs from many other cells, the likelihood of firing at

any one moment depends on the net balance between excitation and inhibition across all of the inputs at that particular time.

Glutamate receptors tend to be located out on the dendrites, especially in the spines, whereas GABA receptors tend to be found on the cell body, or on the part of dendrites close to the cell body. In order for glutamate-mediated excitation to reach the cell body to help trigger an action potential, it has to get past the GABA guard. Excitation coming down a dendrite and headed for the cell body can be extinguished by GABA.

Without GABA inhibition, neurons would send out action potentials continuously under the influence of glutamate, and would eventually literally fire themselves to death. This effect has been demonstrated in experiments where the action of GABA is blocked artificially, or where powerful doses of glutamate-related compounds, too strong to be inhibited by natural levels of GABA, are administered. Overactivity of glutamate, and the resulting injury to neurons, actually plays an important role in stroke and other vascular disorders of the brain, as well as in epilepsy and possibly Alzheimer's disease. Some people have experienced mild versions of glutamate toxicity after eating Chinese food. Monosodium glutamate (MSG), sometimes used as an additive in this cuisine, can increase the amount of glutamate in the body to the point of causing headaches, ringing ears, and other physical symptoms. Regulation of GABA inhibition is one of the ways that psychoactive drugs work. For instance, the antianxiety drug Valium works by enhancing GABA's natural ability to regulate glutamate. Excitatory inputs that would normally elicit anxiety by firing action potentials in fear circuits are less able to do so in the presence of Valium and related drugs.

MOD SQUADS

Interactions between glutamate and GABA are key to understanding information processing by the brain, but these substances do not work alone or in isolation. For example, when receptors in the eye detect patterns of light, they send messages through the axons of the optic nerve to the brain. When the electrical signal reaches the axon terminal, glutamate is released. Whether the postsynaptic cell fires depends not only on the counterbalancing force of GABA inhibition, but also on other chemicals that are present at the time. These are called modulators.

Modulators are neurotransmitters in the sense that they provide a chemical link between the site from which they are released and the location of the

receptors upon which they act. But in contrast to glutamate and GABA, they are less directly involved in the transfer of information from point to point in hierarchical circuits. The way a modulator is distinguished from a transmitter is different for different kinds of modulators, as we'll see soon. And sometimes, the distinction is murky. But one important difference is related to their speed. Glutamate and GABA are fast-acting:[43] they cause an electrical change in the postsynaptic cell within milliseconds of being released from the presynaptic terminal, and their effect is over in a matter of milliseconds.[44] Modulators, on the other hand, have slower and longer-lasting effects.

We'll consider three classes of modulators: peptides, amines, and hormones. Each can have excitatory or inhibitory effects, depending on the specifics of their participation in functional circuits.

Peptides represent a large class of slow-acting modulatory substances found throughout the brain. They are made up of many amino acids, and are larger molecules than simple amino acids like glutamate or GABA. Because peptides are often present in the same axon terminal as glutamate or GABA (but in their own separate storage compartments), they are released with the fast transmitter when an action potential comes down the axon (fig. 3.11). But peptides bind to distinct postsynaptic receptors and can, as a result, augment or reduce the effect of the fast transmitter with which they are released. However, since peptides are slow to affect the postsynaptic site, and their effects are long-lasting, they tend to have more of an effect on subsequent squirts of fast

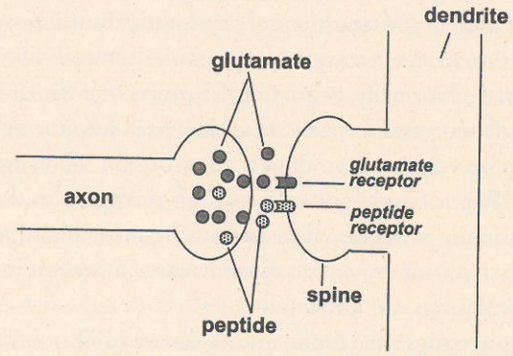

FIGURE 3.11 GLUTAMATE AND PEPTIDE RELEASED FROM THE SAME TERMINAL

Axon terminals sometimes release peptide transmitters along with glutamate (or GABA). In this case, different postsynaptic receptors bind the two kinds of molecules released from the same terminal.

transmitter. While glutamate and GABA can have slow effects as well as fast ones, depending on the receptors involved,[45] peptides typically only have slow modulatory actions. They can affect dramatically the ability of a cell to be fired by other inputs, but cannot do so with precise timing.

There are many, many peptides that participate in a wide variety of bodily functions. Our interest is in the neuroactive peptides, those that act in the nervous system. The best known of these are the opiates—endorphins and enkephalins. These are triggered by pain and stress and bind to their special receptors, altering pain sensations and mood. "Jogger's high" is said to be an opiate effect. Morphine generates its effects by binding to these receptors.

The monoamines, another class of modulators, include substances like serotonin, dopamine, epinephrine, and norepinephrine. Unlike most other transmitters and modulators, the cells that produce monoamines are found in only a few areas, mostly in the brain stem,[46] but the axons of these cells extend to widespread areas throughout the brain (figs. 3.8 and 3.12). In this way, a small number of highly localized neurons making monoamines can influence cells in many other locations. Monoamines achieve their effects by facilitating or inhibiting the actions of glutamate or GABA (and the peptides that are released with them). Because the axons are so widely distributed, monoamines have relatively nonspecific effects. They are thus not involved in precise representation of stimuli in specific circuits. Instead, monoamines produce global state changes in many brain areas simultaneously, such as the high degree of arousal occurring throughout the brain when we encounter a sudden danger or the low degree of arousal required when we are going to sleep.

Many drugs used in the treatment of psychiatric disorders work by altering monoamines. Prozac, for example, prevents the removal of serotonin from the synaptic space. Normally, as part of the process by which transmitter action is regulated, neurotransmitters are sucked back into the terminals that release them. By preventing the removal of serotonin, allowing more to stay around longer, Prozac amplifies its effects. One theory holds that there is a deficiency of serotonin in depressed or anxious brains, which Prozac helps correct.[47] The exact means by which the increase in serotonin levels relieves anxiety or depression is not known.

Antidepressant drugs (like monoamine oxidase inhibitors and tricyclic antidepressants) and antipsychotics (like chlorpromazine or phenothiazine) also work by altering monoamine levels. Amines are also targets of recreational drugs: cocaine and amphetamine affect norepinephrine and dopamine levels, while LSD acts on serotonin receptors.

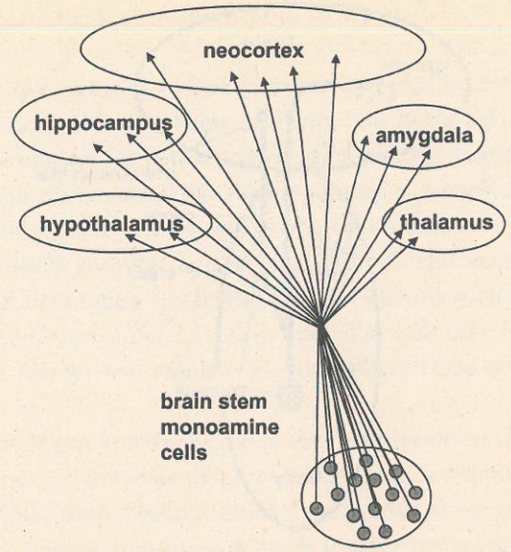

FIGURE 3.12 DIFFUSE PROJECTION OF BRAIN STEM MONOAMINE CELLS TO FOREBRAIN AREAS

Monoamine neuromodulators are made in discrete areas of the brain stem, but because of their diffuse connections, they can simultaneously modulate transmission in widespread areas of the brain.

Another monoamine is acetylcholine, which functions as a fast transmitter when it works with one receptor and as a modulator with a different receptor.[48] Disruption of acetylcholine in the neocortex is believed to play a role in Alzheimer's disease,[49] and many drugs that have been tested as treatments for Alzheimer's alter acetylcholine function.[50] Acetylcholine is also a very important transmitter in the body, involved with nerves such as those that control muscle movements and heart rhythm. Nerve gas works by disrupting acetylcholine transmission at muscles, especially muscles required for normal breathing. Many insecticides have similar effects in bugs.

Hormones are the last class of modulators we will consider (fig. 3.13). Typically, they are released from bodily organs (like the adrenal, pituitary, or sex glands) into the bloodstream where they travel to the brain. There they can, like other modulators, alter the efficacy of glutamate or GABA transmission by binding to specific receptors on cells. For example, cortisol, a steroid hormone released from the adrenal gland during stress, is known to alter informa-

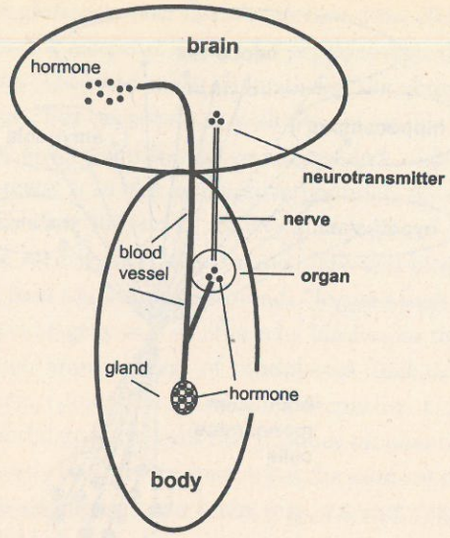

FIGURE 3.13 HOW HORMONES REACH THE BRAIN

Hormones released from glands in the body travel in the bloodstream and either can influence the brain directly or can influence the brain indirectly by acting in body organs that send nerves into the brain.

tion transmission in a variety of circuits involved in memory and emotional processes,[51] in part by altering the ability of GABA to inhibit glutamate.[52] Sex hormones, such as testosterone and estrogen, also can have profound effects on neural transmission and other brain functions. The mood-altering effects of monthly variation in estrogen levels in females are widely discussed, and estrogen replacement therapy during and after menopause is believed to counter some of the effects of aging on brain functions.[53] Because hormones reach the brain through the bloodstream, they can influence many regions simultaneously. However, since only certain areas, and only certain circuits in those areas, possess the relevant receptors, considerable specificity can be achieved by hormonal modulation.

GOLGI AND THE GAP

As important as chemical synaptic transmission is in the brain, another form, called electrical transmission, also occurs. Although the extent to which electrical synapses operate is not known, it is becoming more and more

parent that they are significant forces for us to deal with as we conceive brain function.

In order for two neurons to communicate electrically, their membranes have to fuse in such a way as to allow the direct flow of electricity from one to the other. These points of fusion are called gap junctions. Recent studies have shown that in some brain areas, like the hippocampus, a region important for the formation of explicit memories, GABA (inhibitory) cells are linked together, or electrically coupled, by gap junctions.[54] In this way, when GABA cells are activated, excitation can spread between them in such a way as to activate many of the interconnected cells at once. The cells then fire together, in synchrony, and thereby can regulate activity of projection cells throughout the region.

The existence of gap junctions gives partial vindication to Golgi's reticular theory of the brain, in the sense that some neurons can communicate directly by way of physical fusion. Much remains to be learned about them, and their contribution to synaptic transmission needs to be better integrated with our knowledge of chemical transmission.

CIRCUITS IN ACTION

The same basic transmitters, modulators, and hormones can be involved in very different functions. Our abilities to see, hear, remember, fear danger, and desire happiness all involve excitatory (glutamate) synaptic transmission regulated by inhibitory (GABA) synapses and modulated by peptides, amines, and hormones. What makes a sound different from a sight, a memory different from a perception, a fear different from a desire is not so much the chemistry involved but instead the specific circuits in which the chemicals act. As a way of illustrating how glutamate, GABA, and modulators work, let us consider their role in the detection of danger by the amygdala.

The amygdala detects danger by virtue of its position in a synaptically connected system. In its simplest form, this system can be described in terms of a three-level excitatory chain of cells that releases glutamate—projection cells in sensory systems activate projection cells in the amygdala, which activate projection cells in motor control areas (fig. 3.14). This scheme leaves much out, but we'll have the opportunity to embellish it later.

Amygdala cells receive inputs from the sensory world constantly, but they ignore the majority of them. In fact, they tend to be quiescent most of the time. They do get worked up, though, when the right kind of stimulus is pres-

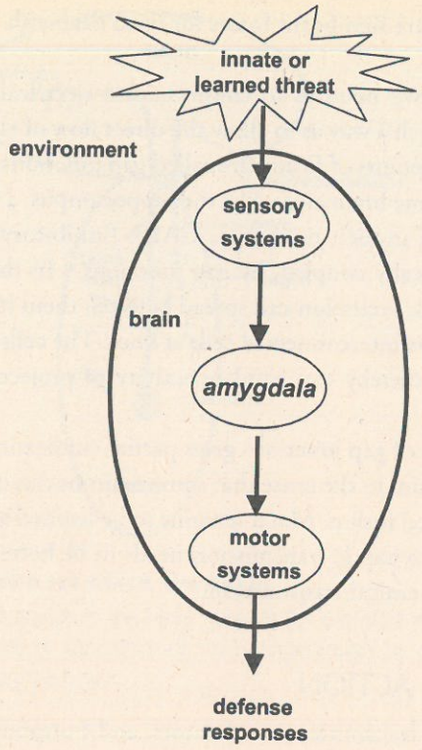

FIGURE 3.14 INPUT AND OUTPUT CONNECTION OF THE AMYGDALA IN FEAR
The amygdala is able to serve as an interface between threatening stimuli in the environment and defense responses because it is connected with sensory processing systems on the one hand and with motor control regions on the other.

This has been shown to be true in studies of both lower animals[55] and humans.[56] So what keeps a projection cell in the amygdala from firing in response to meaningless stimuli? The answer, as you've probably guessed, is GABA.[57]

As we've seen, the resting membrane potential of cells in many brain areas is about −60 mV. In the amygdala, however, some cells can be as negative as −80 mV,[58] due to sustained or tonic inhibition by GABA. With GABA receptors on amygdala projection cells occupied and passing chloride, the inside of the cells becomes more negative, which means it takes extra excitation to turn the amygdala on. As a result, not any old stimulus will do the trick. The stimulus has to have special qualities that allow it to overcome the tonic inhibition produced by GABA.

Stimuli that are inherently dangerous (the sight or smell of a predator) or unpleasant (intense stimuli, like loud noises or stimuli that cause pain) are able to overcome the tonic inhibition, as are stimuli that have emotional resonance acquired through past learning. Thus, an otherwise meaningless sound of modest intensity that previously occurred in association with pain has the same effect as a natural (innate) form of danger.[59] Both innate (hardwired) and learned danger signals cause amygdala cells to fire rapidly for a sustained period, and are thus able to overcome the GABA guard.

Even after fear-arousing stimuli get past tonic inhibition and cause amygdala cells to fire, however, they are still subject to GABA control. The inputs to the amygdala activate GABA cells as well as projection neurons.[60] As a result, as the inputs become more active, the elicited inhibition in the amygdala builds up, which in turn begins to shut down the activity of amygdala cells.[61]

If the ability of GABA to keep meaningless stimuli from turning on the amygdala is compromised for some reason (either because the projection cells come to fire more easily or because the GABA cells fire less easily), stimuli that are not dangerous come to be responded to as though they were. This may occur in certain fear and anxiety disorders. By the same logic, things that make projection cells fire less readily or that make GABA cells fire more readily should reduce fear and anxiety. Indeed, one of the most popular medications ever invented for the treatment of anxiety is Valium, which works by facilitating GABA transmission. Although drugs taken orally reach many sites in the brain, it is likely that at least some of their effects on fear and anxiety are achieved by enhancing inhibition in the amygdala, and thereby making it harder for external or internal stimuli to elicit fear responses by activating amygdala circuits.

The amygdala also receives modulatory inputs of various types. For example, serotonin fibers terminate there, and when the amount of serotonin rises in the amygdala the activity of excitatory projection cells is inhibited.[62] The inhibition in this case is not due to the fact that serotonin directly affects projection cells, but rather that serotonin excites GABA cells, and thus increases the degree to which they inhibit projection neurons.

Drugs like Prozac work by increasing the amount of serotonin available at synapses. By enhancing serotonin transmission at GABA synapses in the amygdala, and thereby reducing the activity of projection neurons, Prozac may, like Valium, help control anxiety by reducing the ability of inputs to the amygdala to activate fear circuits.

The amygdala is also the target of many hormones. One of these is cortisol, which is released from the adrenal cortex during fear-arousing and other-

CHAPTER FOUR

BUILDING THE BRAIN

EACH CHILD IS AN ADVENTURE INTO A BETTER LIFE—AN OPPORTUNITY TO CHANGE THE OLD PATTERN AND MAKE IT NEW.

—Hubert H. Humphrey

The brain's billions of neurons are intricately connected in ways that make possible the mundane (such as the regulation of breathing) and the marvelous (the belief in an idea). But how do cells in the developing embryo become neurons, and how do they end up in just the right places? How do the axons of all these cells find their way to their target areas? And once having reached them, how do the terminals figure out exactly which neurons to make synapses with? Because the various steps take time, and because different circuits go through these steps on different schedules, our behavioral and mental repertoire unfolds gradually, and unevenly, during childhood. Somehow, though, it all comes together, and a person, a self with all its aspects, emerges.

Brain development is the major battlefield of the nature-nurture conflict. In its simplest form, the debate is about whether mental and behavioral characteristics are determined more by genes or by environment. To the extent that mental and behavioral characteristics are functions of the brain, and synaptically connected circuits underlie brain functions, the nature-nurture debate essentially reduces to questions about how circuits are built during development.

No one today seriously proposes that the brain is a blank slate at birth,