CHAPTER 2
THE BRAIN

KEY THEMES

- The central nervous system (CNS) is organized into four parts: the spinal cord; the brainstem; the cerebellum; and the cerebrum.
- The computational elements of the brain are its neurons, whose cell bodies are primarily located in cortex, on the outside surfaces of the cerebrum and cerebellum, as well as in subcortical nuclei.
- The neocortex of the cerebrum is organized in six layers, each of which has a distinct functional role.
- The neuron has three principal components: the cell body; the branching dendrites, which receive signals from other neurons; and the projecting axon, which sends signals to other neurons.
- Neurons maintain electrical and chemical disequilibria in relation to the surrounding extracellular space, and many neuronal properties and processes can be understood in terms of the maintenance of these disequilibria.
- Neurons transmit information to other neurons via electrical action potentials that are propagated along axons.
- These electrical action potentials are converted to chemical signals – the release of neurotransmitter – at the synapse, the interface between the "sending" and the "receiving" neuron.
- Different types of neurons release different neurotransmitters, some of which have excitatory (depolarizing) effects on the postsynaptic neuron, some of which have inhibitory (hyperpolarizing) effects on the postsynaptic neuron.
- The net effect on a neuron receiving different types of neurotransmitter that can be released at different moments in time is that its membrane potential oscillates.
- The coordination and control of oscillations in different populations of neurons may be an important way that the flow of information in the brain is controlled.

Essentials of Cognitive Neuroscience, First Edition. Bradley R. Postle

CONTENTS

PEP TALK

Thinking, consciousness, decision making, language; these, and topics like them, are what you're expecting to learn about in this book. And you will. But for our explorations to be substantive, it's necessary that we establish a foundation of knowledge about how the brain is organized, structurally, and how it works. This necessitates the present chapter, which will cover neuroanatomy and cellular and circulatory neurophysiology, with little to no consideration of behavior. Thus, the following pages may be tough sledding for some readers who, for example, may have some background in psychology, but not in biology. But it will be good for you! And we just can't get around it. For example, understanding the physiology of the neuron is critical for interpreting neuroimaging data, because whereas some methods measure electrical fluctuations, others measure changes in blood oxygenation, and others measure changes in the reflectance of light. Thus, valid interpretation of data from a neuroimaging study of, say, face recognition, or emotion regulation, will depend critically on understanding what aspect of brain activity it is that is generating the signal that we are interpreting.

Later in this book, we'll see that one of the traits supported by the prefrontal cortex (PFC) is the ability to choose to engage in behavior for which the reward may not be immediate, but for which it will be worth the wait. And so, in that spirit, let's keep our eyes on the prize, and dive in!

GROSS ANATOMY

Like much of the rest of the body, most parts of the brain come in twos. There are two hemispheres, and within each hemisphere there are the five lobes of the **cerebrum** – four of them named after the four bones of the skull under which they lie (frontal, parietal, occipital, and temporal), plus the deep-lying limbic lobe, which is not adjacent to the skull (*Figure 1.2*). The brain belongs the central nervous system (often abbreviated CNS), which also comprises the spinal cord and the motor neurons that leave the cord to innervate the muscles of the body. All of these elements derive, during development of the embryo, from the neural plate, a two-dimensional sheet of tissue that folds until its edges touch and merge to form the neural tube. In primates, which are bipedal, the CNS makes a right-angle bend between the midbrain and the forebrain such that, when standing erect, the spinal cord, brainstem, and midbrain are oriented vertically, and the **diencephalon** (**thalamus**) and cerebrum are oriented horizontally. Thus, for a standing human, whereas the directional terms *dorsal* and *ventral* refer to the "back" and "front" of the spinal cord, they refer to the "top" and "bottom" of the brain (*Figure 2.1*).

When you look at a brain that's been dissected out of a skull the first thing that you notice is how wrinkly it is (*Figure 1.2*, *Figure 1.4*, and *Figure 2.2*). The reason for this makes sense once you understand two facts. The first is that the computational power of the mammalian brain is in the cerebral **cortex** – the thin (roughly 2.5 mm thick) layer of tissue that covers the outside surface of the five lobes of the cerebrum – and in the cortex of two other structures, the **hippocampus** and the cerebellum. (For ease of exposition, this introductory section will focus on cerebral cortex.) The second is that the cerebral cortex is, in effect, a two-dimensional sheet, with a surface area of roughly 2500 cm^2. Indeed, if one could "unfold" and flatten out the cortex, it would take roughly the same surface area as a tabloid-style newspaper. (In Madison, WI, where I work and teach, I use the example of the satirical newsweekly *The Onion*, but you can pick your favorite rag.) Now we can return to the wrinkles, realizing that "crumpled" might be a better descriptor: over the course of evolution, as the computational power of the brains of vertebrate species has increased, the ever-larger cerebral cortex has needed to fold ever-tighter onto itself in order to fit inside the roughly spherical skull. The alternative, evolving a thin, 50 cm × 50 cm square (or comparably sized disk) for a skull might look okay on a creature from one of those sci-fi anime cartoons that my son watches on television, but would clearly be highly inefficient, particularly from the standpoint of the amount of "wiring" that would be needed to connect different parts of the brain together. In contrast, it has been calculated that the "crumpled up" solution with which we have evolved yields a cerebrum that is almost optimally shaped to minimize connection distances between different groups of neurons.

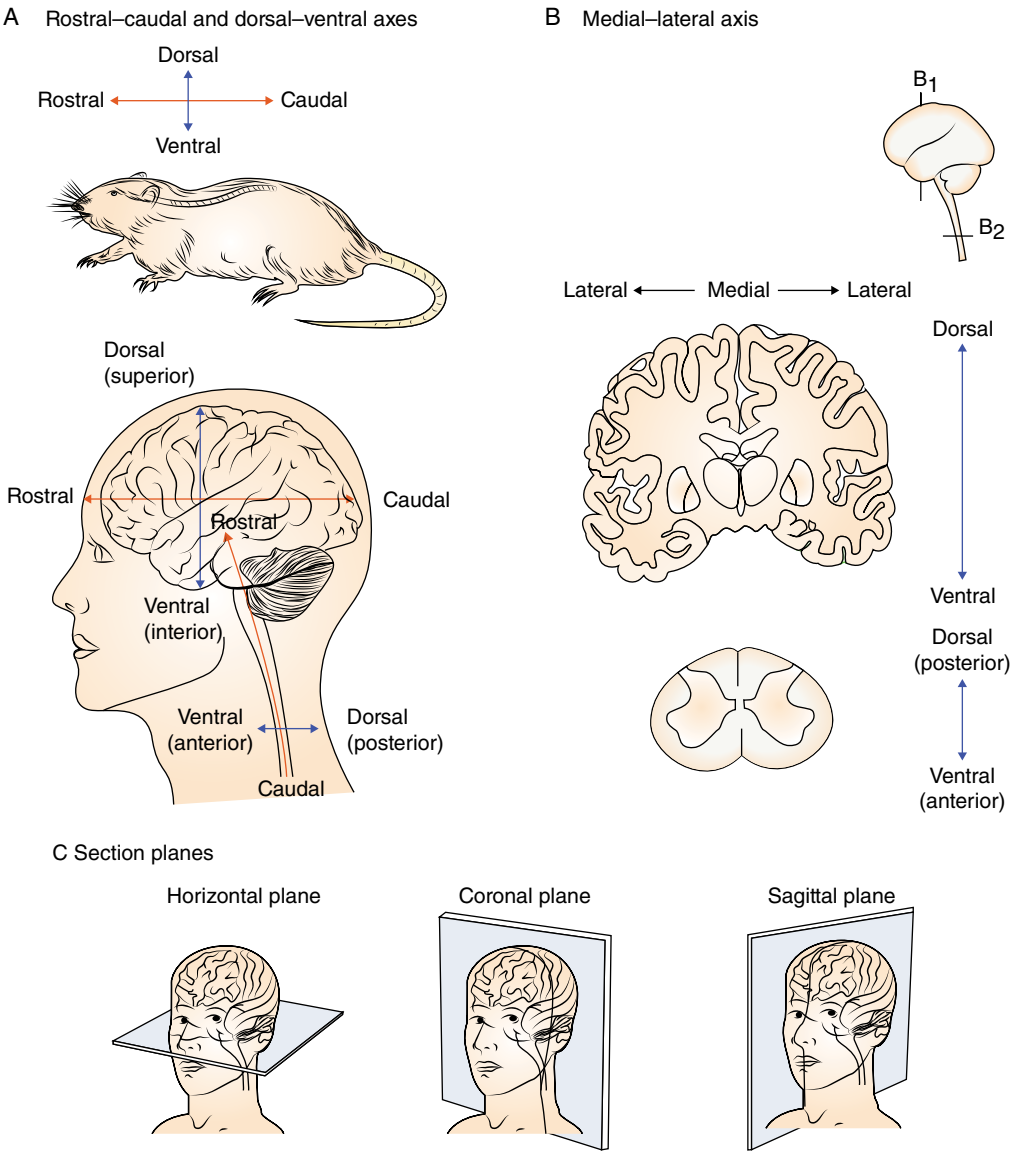

FIGURE 2.1 Terminology for anatomical orientation. **A.** The quadruped. **B**. In the bipedal human, the terminology is complicated by the right-angle bend that the neuroaxis makes between the midbrain and forebrain. **C.** The cardinal planes of section. Source: Kandel, Schwartz, and Jessell, 2000. Reproduced with permission of McGraw-Hill.

When the brain is sliced, you see that the cortex looks darker (**gray matter**; although to me it looks more taupe than gray …) than the **white matter** that takes up most of the volume of the brain (*Figure 2.2*). The gray matter is the aggregation of hundreds of thousands of brain cells – neurons and "supporting" cells known as **glial cells**. All neurons have a branch via which they communicate with other neurons. These branches, called **axons**, conduct electrical signals that are fundamental to how neurons communicate.

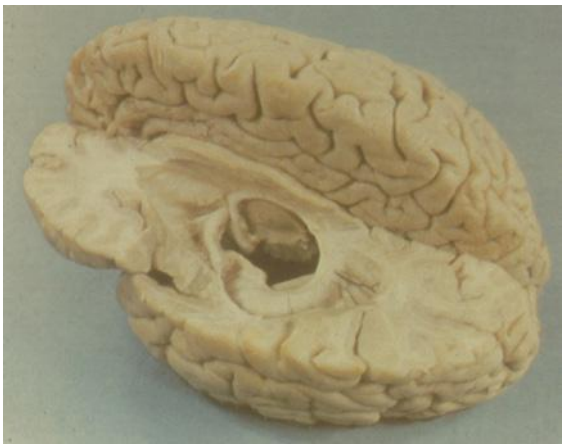

FIGURE 2.2 Human brain with dorsal half of left hemisphere dissected away with a cut in the axial plane to reveal several subcortical anatomical features. Along the medial surface of the temporal lobe is the hippocampus, and the fibers projecting from its medial edge make up a tract called the fornix, which forms an arc as it courses rostrally from the caudal end of the hippocampus to terminate at the mammillary bodies of the hypothalamus. Immediately rostral to the rostral-most extent of the fornix, and to the rostral end of the hippocampus, is the anterior commissure, running in a mediolateral-oriented tract carrying transhemispheric axons between the anterior temporal lobes. Finally, the medial aspect of thalamus of the right hemisphere appears as though it is immediately ventral to the arc of the fornix. (Use the *Web 3-D Brain* to help identify these structures.) The surface of the axial cut also reveals the depth of many sulci (lined with gray matter), including the intraparietal sulcus at the caudal end of the brain. Source: Warwick and Williams, 1973. Reproduced with permission of Elsevier.

Just like the electrical power lines that carry electricity from power plants to the places where the electricity is needed, axons are insulated, so as to conduct electrical current efficiently. In the brain, this insulation is a cholesterol-laden substance called **myelin**, and the aggregation of millions of myelinated axons is what makes the white matter look white. As illustrated in *Figure 2.1*, there are three cardinal planes along which brains are sliced: in vertical cross section ("coronally"); in horizontal cross section ("axially"); or vertically along the long axis ("sagittally"). From the coronal section, in particular, as well as from *Figure 2.2*, one can appreciate many of the brain's "wrinkles" are quite deep. The technical term for the wrinkles is **sulci**. Indeed, if you were to hold a human brain in your hand and rotate it so that you could inspect it from every angle, you'd only be able to see about one third of the cortical surface. Two thirds are "hidden" along the walls of sulci, or lining the "middle" walls of each hemisphere. In inspecting a brain like this you'd be viewing its *lateral* (i.e., "toward the outside edge") surface. Regions nearer to the center of the volume are said to be *medial*. The "bumps" and "ridges" that are visible in the intact brain are referred to as **gyri**. The dissection featured in *Figure 2.2* provides a "window" revealing several regions of gray matter that are medial to the cortex (i.e., deep "inside" the brain). Most of these subcortical structures are nuclei – collections of cell bodies that all perform a related function. Also visible in *Figure 2.2* are large bundles of myelinated axons. The largest, the corpus callosum, carries millions of axons projecting from one hemisphere to the other.

> **Tip 2.1**
> In the monkey (and sometimes in the human), the sulcus analogous to the Sylvian is often referred to as the "lateral fissure."

Let's return to the visual inspection of the intact brain that we are holding in our hands. The most obvious landmark is the midline, the gap separating the two hemispheres. From the canonical "side view" (as in *Figure 1.2*) we see the two prominent sulci that more-or-less divide the rostral from the caudal half, and we see the distinctive temporal lobe that is located ventrally and oriented parallel to the rostral-caudal axis. The sulcus that forms the dorsal boundary of the temporal lobe is the Sylvian fissure (a fissure being a really big sulcus); the sulcus that's parallel to the caudal-most section of the Sylvian fissure, and roughly two gyri rostral to it, is the central sulcus. As its name implies, the central sulcus divides the "front half" from the "back half," the frontal lobe from the parietal lobe. We shall see that, in functional terms, this anatomical landmark also demarcates, to a first order of approximation, the fundamental distinction of "action" (frontal) vs. "perception" (parietal, temporal, and occipital) (*Tip 2.1*). The occipital lobe, the caudal-most in the

REAL-WORLD APPLICATIONS

2.1 Myelination in development and disease

Although their authors may not know it, many laws and rules that govern modern society are influenced by one particular fact of brain development: whereas much of the circuitry of the prefrontal cortex (PFC; *Figure 1.2*) is in place by the time we reach puberty, axons responsible for transmitting signals within and from this region aren't fully myelinated until considerably later. Other neurodevelopmental processes, such as the growth of **dendrites** and development of **synapses**, also take longer to complete in PFC relative to other brain areas. This developmental lag has profound implications for behavior. The functions of the PFC won't be examined in detail until later chapters, but for the time being suffice it to say that the PFC plays a critical role in our ability to control our behavior, such as the ability to inhibit impulsive responses in favor of longer-term goals, and the ability to guide our actions according to abstract rules (e.g., laws, social conventions, long-term goals) rather than by simply responding to whatever is in front of us at a given moment in time. Thus, the developmental lag in the myelination of the PFC contributes to the fact that teenagers are statistically more likely to engage in risky behavior, and will typically be more impulsive and unpredictable than will be individuals in their mid-20s who are drawn from the same population. As a result, the developmental lag of PFC myelination can be seen as a root cause of the fact that many automobile rental companies won't rent to individuals younger than 22, and for why the age at which one can legally purchase alcohol in many parts of the United States is 21. At the other end of the developmental spectrum, the loss of myelin is a hallmark of normal aging, and can be accelerated in some neurodegenerative disorders such as Alzheimer's disease. Indeed, just as the PFC is among the last regions of the brain to fully myelinate as humans move into young adulthood, it is also among the first to begin demyelinating as they move into middle age.

Clinically, abnormal patterns of demyelination are the basis for many neurological diseases. In the CNS, the most well-known demyelinating disease may be multiple sclerosis (MS). Like many other demyelinating diseases, multiple sclerosis is the result of an abnormal immune response in which the immune system attacks the oligodendrocytes whose arms create the myelin sheath around axons. Symptoms of MS vary widely, depending on which part(s) of the CNS are affected, and can range from blurred vision (due to demyelination of axons traveling from the retina to visual nuclei of the thalamus) to movement disorders (due to demyelination of axons carrying movement-related signals in the spinal cord). MS can also impair cognition. In the **peripheral nervous system**, Guillain–Barré syndrome is also caused by an immune response that compromises the integrity of myelin. It is typified by weakness or paralysis in the extremities that migrates to the trunk. In addition to discomfort and movement problems, it can be life-threatening if it affects parts of the autonomic nervous system, such as the neurons that control breathing.

brain, sitting atop the cerebellum, has the least obvious boundaries with the two lobes with which it makes contact on its lateral surface, the temporal lobe, ventrally, and the parietal lobe, dorsally.

The tissue connecting the two hemispheres is the thick band of fibers (i.e., axons) that connect neurons of the left hemisphere to those of the right, and vice versa. This is the **corpus callosum**. If one severs the corpus callosum, so as to separate the two hemispheres, one can then inspect the medial surface of either hemisphere (a so-called midsagittal view; *Figure 1.2.B*). This reveals the fifth lobe of the brain, the limbic lobe, which consists primarily of the anterior cingulate gyrus and the posterior cingulate gyrus, the gyri that surround the corpus callosum in its rostral and caudal aspects, respectively (*Figure 1.2.B* and *Figure 2.2*).

Very prominent in the middle of the brain, whether sliced axially, coronally, or sagittally, is a large gray-matter structure called the thalamus. Fittingly, the thalamus acts as a hub for the brain: all incoming sensory information (with the exception of olfaction) is relayed through the thalamus on its way to the cortex. Additionally, the thalamus acts as a node in several circuits, sometimes called "loops," in which information cycles from cortex to thalamus and back to cortex again (in some cases with several other subcortical connections interposed). More detail about the anatomy and functions of these "corticothalamic" loops will be considered in subsequent chapters of the book. Because it is so intricate, and is organized anatomically according to the different brain systems with which it connects (e.g., the visual system, the auditory system, the prefrontal cortex), the thalamus is itself considered to be made up of several nuclei. Throughout the book, as we consider different systems and/or functions, we'll also look more closely at the relevant thalamic **nucleus** (e.g., the lateral geniculate nucleus (LGN) for vision, the medial geniculate nucleus (MGN) for audition, and the mediodorsal (MD) nucleus for prefrontal cortex).

Finally, from any of the dissections that reveal the thalamus one can also see the hollow chambers that take up a considerable portion of the intracranial volume. These are the **ventricles**, the largest being the lateral ventricle. In the living organism the ventricles are filled with the **cerebrospinal fluid (CSF)** that bathes the brain on its inside (i.e., ventricular) and outside surfaces. On the outside, it circulates between a thin layer of tissue that lies on the surface of the cortex – the pia mater – and the arachnoid membrane, so named because it suggests the appearance of a spider web. Enclosing the arachnoid membrane is the rubbery dura mater, and, finally, the bone of the skull. Together, the dura, arachnoid, and pia are referred to as the meninges. (Meningitis is the infection and swelling of this tissue.) The CSF is under pressure, such that it gently inflates the brain from within the ventricles, and it is in continuous circulation through the ventricles and down the entire length of the spinal cord. For this reason, CSF extracted via a procedure called a lumbar puncture (a.k.a. a "spinal tap"), can be assayed to assess certain measures of brain health. For example, elevated levels of certain proteins in the CSF may signal excessive cell death, as happens in Alzheimer's disease.

The section that you have just read may well be the one that will benefit the most from *Web Link 1.1*, the 3-D brain. The book's companion Web site also contains images from brain scans, particularly magnetic resonance (MR) images, which are the focus of *Methodology Box 2.1*, *Web Clip 2.1*, and *Web Clip 2.2*. (In addition I strongly encourage you seek out an opportunity to have the hands-on experience of holding a brain and, if possible, dissecting it. Often, especially in a formal class, the dissection will be performed with the brain of a sheep. At the level of the gross anatomy you'll find all the structures that have just been described, and the experience will generalize to any vertebrate species (including humans) that you may subsequently study in more depth.)

The cerebral cortex

The cerebral cortex is also referred to as neocortex, in reference to the fact that it is a relatively new feature of the CNS in evolutionary terms. It is made up of six layers, which are visible when a very thin slice of cortex is viewed under a microscope. The reason that these layers look different is that each is made up of different types of cells and/or tissue that serve different functions (*Figure 2.3*).

The central layer, layer IV, is the layer that receives input from the thalamus. Thus, in the case of primary visual cortex ("area V1"), for example, the neurons of layer IV are the first cortical neurons to begin processing signals relating to, say, the photons reflecting off this page of the book. Layers II and III have subtle differences, but for the purposes of this textbook they can be thought of as being functionally equivalent, and will often be referred to as "layer II/III." The property of layer II/III that will be emphasized here is that neurons from this layer tend to be those that send information to higher levels of cortex. As illustrated in *Figure 2.4*, it is neurons of layer II/III of the second visual processing area ("V2") that project to a higher-level visual processing area ("V4"). (More detail on what is meant by "project to" is considered in the next section, *The Neuron*; more details on the organization of the visual system are in *Chapter 3*.) Because the flow of visual information can be construed as traveling

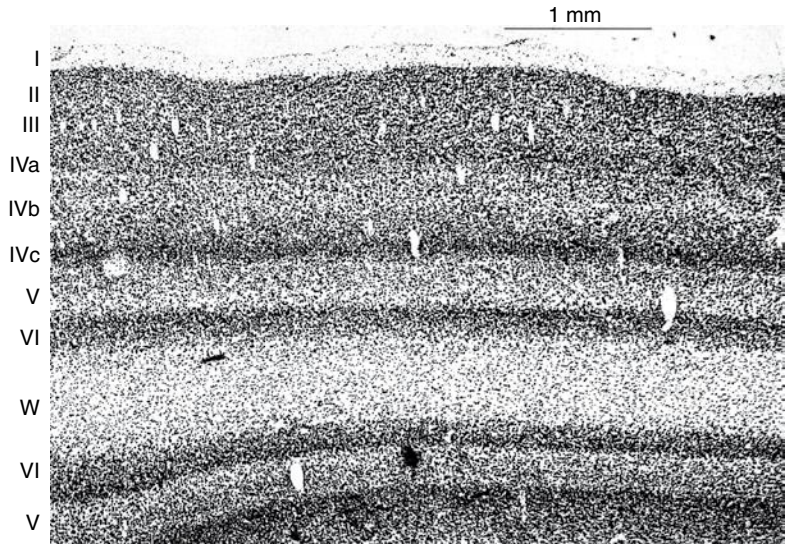

FIGURE 2.3 Cross-sectional view of cortical area V1 of the macaque, illustrating the six layers, including several subdivisions of layer IV. The tissue is from a narrow gyrus such that, at the bottom of the image, below the region of white matter (labeled "W"), one sees the deep layers of a nearby area of cortex. Source: Hubel and Wiesel, 1977. Reproduced with permission of the Royal Society.

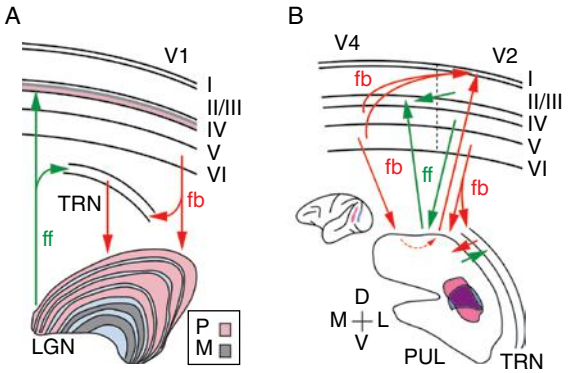

FIGURE 2.4 Schematic illustration of thalamocortical and corticocortical feedforward (ff) and feedback (fb) projections. Panel **A** illustrates the projections from the lateral geniculate nucleus (LGN; diagrammed in cross section) of the thalamus to layer IV of V1, and from layer VI of V1 back to the LGN. Note that there are six primary layers of the LGN, four containing parvocellular (P) neurons and two containing magnocellular (M) neurons (to be detailed in *Chapter 3*), and that these two types of LGN neuron project to different sublayers of cortical layer IV (to be detailed in *Chapter 5*). Also to be detailed in *Chapter 3* will be the role of the thalamic reticular nucleus (TRN), which receives collaterals from the axons carrying feedforward and feedback signals. Panel **B** illustrates the organization of feedforward and feedback pathways between two higher levels of visual cortex, areas V2 and V4 (*Tip 3.3*). "Direct" corticocortical feedforward projections go from layer II/III of V2 to layer IV of V4. "Indirect," thalamically mediated feedforward projections go from layer V of V2 to the pulvinar nucleus of the thalamus (PUL) and then from pulvinar to layer IV of V4. Direct corticocortical feedback projections are illustrated as going from layers V and VI of V4 to layer I of V2 (the laminar specificity for this and other interareal projections varies across brain systems and across species). Indirect feedback projections go from layer VI of V4 to the pulvinar nucleus, and then from pulvinar to layer I of V2. The small diagram of a lateral view of the macaque brain relates to how these data were generated, and will be more easily understood after reading *Methodology Box 2.2*. It shows where anterograde tracer was injected into areas V4 (pink) and V2 (blue), and the diagram of a coronal slice through the pulvinar nucleus shows the overlapping projection zones from these two cortical regions. Source: Images provided by Y. Saalmann and adapted by author; see Saalmann and Kastner (2011) for more detail. Reproduced with permission of Elsevier.

Tip 2.2
For reasons unknown to this author, the layers of cortex are often written with Roman, rather than Arabic, numerals.

Tip 2.3
A generic noun for a nerve fiber, if one doesn't want to specify whether it is an axon or a dendrite, is *process*.

from the retina to the LGN of the thalamus, from thalamus to V1, from V1 to V2, and from V2 to V4, the layer II/III projections from V2 to V4 are considered feedforward connections. The neurons of layers V and VI tend to be those that send feedback projections to earlier levels of cortex. (Depending on the region of the brain, corticocortical feedback projections may arise predominantly from layer V or from layer VI.) Finally, neurons from layer VI (and sometimes also layer V) tend to be those that send their projections to the thalamus, or to other subcortical structures (*Figure 2.4; Tip 2.2*). (Note that this and the subsequent paragraph are referring to **pyramidal cells**, one of the two general classes of cortical neurons that will be described in more detail in the ensuing section, *The Neuron*.)

As we shall see in the next paragraph, it's often convenient to refer to one layer of cortex as being "above" or "below" another (as in *layer IV is located below layer II/III*). The reason that this can be problematic, however, is evident from inspecting the cartoon of a coronal slice illustrated in *Figure 2.1*. If we consider the cortex located on the ventral surface of the Sylvian fissure, and thus defining the dorsal boundary of the temporal lobe, layer II/III is, indeed, above layer IV (e.g., it is closer to the top of the page). For the cortex just dorsal to it, however, on the dorsal surface of the Sylvian fissure, the opposite is true, in that layer IV in this bit of cortex is closer to the top of the page than is layer II/III. This is a simple consequence of the fact that the "crumpled" nature of cortex means that portions of it are oriented in virtually every direction possible. A constant property of the layers of cortex, however, no matter in what part of the brain, or whether the owner of that brain is standing upright, lying on his or her back, etc., is that layer II/III is always closer to the surface of the cortex and layer IV is always closer to the white matter. Thus, their positions relative to each other are most accurately referred to as being superficial (closer to the surface) or deep (further from the surface).

And what about layer I? Layer I is distinctive from all other layers of cortex in that is contains very few cell bodies. Instead, it is made up primarily of the "antennae" (dendrites) reaching from layer II/III neurons so as to receive messages being sent by neurons in other regions (*Tip 2.3*). Indeed, this property of neurons with cell bodies located in one layer having dendrites that extend to another layer is common in all layers of cortex. Another important fact about cortical neurons is that, in addition to the properties of receiving thalamic input, sending feedforward projections, or sending feedback projections, many also send projections to other neurons located in the layer(s) above or below. As a result, groups of neurons that are "stacked" on top of each other (from layer II/III to layer VI) can often be characterized as forming **cortical columns**. As this designation implies, neurons are more strongly interconnected with other neurons within the same column than they are with neurons that are immediately adjacent but do not belong to the same column. This principle of "columnar organization" will be important for understanding the principles of visual information processing (*Chapter 3* and *Chapter 5*) and auditory and somatosensory information processing (*Chapter 4*), and may also be important in brain areas that process higher-level information (e.g., the PFC, *Chapter 14*). A final fact about the layers of cortex: depending on the region of the brain, corticocortical connections can terminate in layers I, II/III, and/or V. At this point, however, we've gone about as far as we can go without addressing the questions *What is a neuron? What are its functional units? How does it work?*

THE NEURON

The elements that give the brain its unique properties are the cells that make it up. Recall from earlier in this chapter that there are many, many different types of

cells in the brain, and that many of these are not neurons. For the time being, however, we'll focus on just two classes of cortical neurons: pyramidal cells, and interneurons. The pyramidal cell is the canonical neuron. Its large cell body has a three-dimensional shape that resembles a pyramid, with antenna-like dendrites sprouting from the cell body, particularly its pointy "top," and the axon leaving from the base of the cell (*Figure 2.5*). Typically, the dendrites, like the branches of a tree, spread themselves out over an area much larger than that taken up by the cell body itself (the cell body being the trunk in this analogy). The function of dendrites is to receive messages from other neurons (i.e., it is along dendrites that connections are formed with axons from other neurons). The axon, as we've already discussed, conveys signals from the neuron in question to other neurons. So let us now consider the nature of these electrical signals.

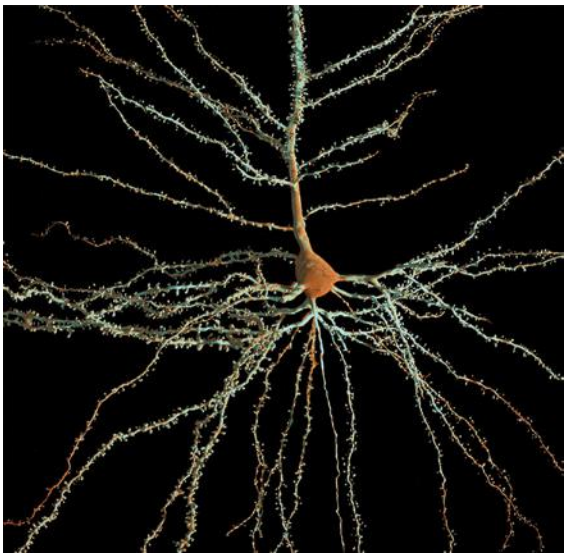

FIGURE 2.5 A pyramidal neuron from layer III of the prefrontal cortex of a monkey. Branching out from what would be the corners at the base of the pyramid-shaped soma are the basal dendrites, and projecting up toward the top of the page is the trunk of the apical dendrite, which will branch extensively when it reaches layer I (not shown). Each dendritic branch is studded with spines, submicron-sized protrusions at the end of which a synapse is formed with an axon. Extending from the base of the soma and projecting straight down and off the bottom of the image is this neuron's axon, distinguishable as the only process that is not studded with spines. To generate this image, the neuron was first microinjected with a dye, then images were acquired with a laser confocal microscope. For details about the method, see Dumitriu et al. (2011); the *Further Reading* from Morrison and Baxter (2012) demonstrates the use of this method to study the effects of aging in the prefrontal cortex. Source: Image courtesy of John H. Morrison, PhD. Reconstruction done by The Visual MD.

Electrical and chemical properties of the neuron

It may be difficult to find a single definition of "life" that any two people would find fully acceptable. Nonetheless, one (perhaps narrowly reductive) stab at a definition would be a system that is able to actively maintain itself in a high-energy state. This is a definition that draws on thermodynamics, in that it invokes the general tendency for objects in our universe to dissipate (or acquire) energy so that their own level of energy matches that of the surrounding environment. As one example, food that is removed from a hot oven and left on the countertop will cool until its temperature matches that of the kitchen. Similarly, food taken out of the freezer and left on the countertop will warm up until it achieves room temperature. In terms of their temperature, these nonliving objects passively give off or take on energy until they reach an equilibrium, which is the temperature of the kitchen. Neurons maintain life by maintaining a *dis*equilibrium along two dimensions, electrical and chemical. With regard to the former, a neuron in its baseline state will maintain a negative voltage of approximately −70 millivolts (mV) relative to the extracellular space that surrounds it (see *Tip 2.4*). It achieves this by maintaining a relatively lower concentration of positively charged ions relative to the extracellular space. In addition to

Tip 2.4
Note that the resting potential of –70 mV refers to a generic neuron. Different cell types will have different resting potentials.

this electrical disequilibrium, the neuron at rest maintains a chemical disequilibrium by "hoarding" a high concentration of potassium (K^+) ions relative to the extracellular space, and maintaining a relatively low concentration of sodium ions (Na^+) relative to extracellular space. (Recall that the membranes of all cells in the body are made up of a lipid bilayer that, because it repels water, separates the watery cytoplasm (and all dissolved in it) inside the cell from the watery extracellular fluid (and all dissolved in it).)

Hey, did someone say "watery extracellular fluid"? That's a cue to discuss **diffusion tensor imaging** (DTI), a tool for in vivo neuroanatomy research (see *Methodology Box 2.1*).

METHODOLOGY BOX

2.1 MRI and DTI – methods for in vivo neuroanatomy

T1-weighted MRI Nuclear magnetic resonance (NMR) refers to the fact that the *nucleus* of an atom (a proton, in the case of hydrogen), *resonates* at a preferred frequency when in the presence of a strong *magnetic* field. For our purposes, we can understand this as owing to the fact that an "unpaired" nucleus (i.e., no neutron paired up with the H atom's lonely proton) rotates. In the jargon of nuclear physics, this rotation is a "spin." NMR imaging, now commonly referred to as magnetic resonance imaging (MRI, see *Tip. 2.5*), is based on the fact that the application of a radiofrequency (RF) pulse at just the right frequency – the resonant frequency of the H atom – can perturb the axis around which the proton is spinning. Because the atom is in the presence of a strong magnetic field produced by the MRI scanner (the "B_0" field, pronounced "bee naught"), the low-energy state for that atom is for the axis of its "spin" to be aligned with that magnetic field. (In MRI, this is the field whose strength is measured in units of tesla, resulting in scanners being labeled, for example, "1.5 tesla" (T), or "3T" scanners.

Now, where were we … Oh, yes … In the process of returning from the higher-energy state into which it has been pushed by the RF pulse, to the low-energy state of alignment with the B_0 field (a process referred to as "relaxation"), the H atom gives off energy. It is this energy that creates the MR image. Different ways of delivering the perturbing RF pulse, referred to as pulse sequences, can influence nuclear spins in different ways, and thereby emphasize different types of tissue. Additionally, different ways of measuring the relaxation signal can yield different kinds of information about the tissue being imaged. One component of this signal, the T1 component, is particularly well suited for distinguishing white matter from gray. This is illustrated in *Figure 2.6*, which features a "T1-weighted" image of a virtual slice through a brain. T1-weighted images ("T1 images," or, sometimes, "T1s" for short) are the most common structural MR images that one encounters in the cognitive neuroscience literature. (More detail and examples in *Web Clip 2.1* and *Web Clip 6.2.*)

DTI tractography Here's where the watery extracellular fluid comes in. Within tracts of myelinated axons there are teeny gaps between each axon. As a consequence, water molecules travel much more quickly along such a bundle than across it. This motion, or *diffusion*, of water molecules can be measured with a particular kind of pulse sequence. The resultant data take the form of a 3-D volume (called a *tensor*) that indexes how symmetrically, or otherwise, water molecules in a particular location within the brain are diffusing. A perfectly spherical tensor, said to be "isotropic," would indicate that water is diffusing freely in all directions. Fiber tracts, in contrast, produce "anisotropic" tensors shaped more like a rugby football. By estimating the most probable route that a series of such tiny end-to-end "footballs" makes through a

Methodology Box 2.1 *Continued*

section of brain, one can infer the existence of a fiber tract, as illustrated in *Figure 2.6*. (More detail and examples in *Web Clip 2.2*.)

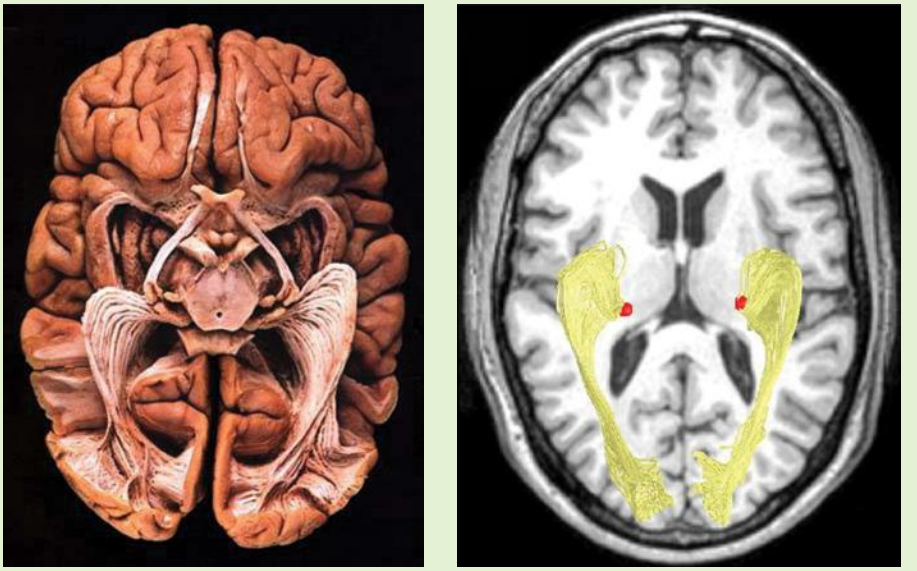

FIGURE 2.6 Image on left shows a human brain dissected to reveal the pathways from retina, via LGN, to V1. Particularly striking are the elegant optic radiations, the myelinated fibers running between the thalamus and the primary visual cortex. To expose these pathways and structures, the anatomist dissected away tissue from the ventral surface of the brain, up to and including the ventral bank of the calcarine fissure. Thus, only the dorsal bank of the calcarine and the fibers of the optic radiations that project to it are seen here. (Some of this will make better sense after having read the first section of *Chapter 3*.) The image on the right shows a slice from a T1-weighted anatomical MR scan (grayscale) oriented to include both the LGN (pseudocolored red) and the calcarine sulcus. Superimposed, in yellow, is an image of the path of the optic radiations as estimated via MR-derived diffusion tensor imaging (DTI) tractography (see *Web Clip 2.1* and *Web Clip 2.2*). Source: Wandell and Winawer, 2011. Reproduced with permission of Elsevier.

Tip 2.5

There is nothing radioactive about NMR. However, because the word "nuclear" can provoke strong reactions (particularly in someone about to undergo a medical imaging procedure!), the alternative "MRI" has become the more common term in the context of medical imaging.

The consequence of the electrical and chemical imbalances in the neuron is that if a hole were to be poked in the membrane of a neuron, two events would happen: (1) the electrical gradient would be reduced by an influx of positively charged ions into the cell (including Na^+ ions); (2) simultaneously, the chemical gradient would be reduced by an efflux of K^+ from the high-K^+ concentration inside the cell to the low-K^+ concentration outside the cell. (And note

Tip 2.6

Because the resting potential of the neuronal membrane is negative, the convention is to say that a current whose effect is to move this potential closer to 0 mV is a *depolarizing* current, and a current whose effect is to move the potential further from 0 (i.e., making it more negative) is a *hyperpolarizing* current.

that the influx of Na^+ ions from (1) would also be reducing the chemical gradient.) As you might imagine, however, the workings of the neuron are much more orderly and regulated than the poking of holes. Indeed, the membrane of the neuron is punctuated with channels that can open and close, thereby allowing the passage of certain types of ions. Most of these channels have differential permeability to different types of ions, and are only activated under certain conditions. One example is the voltage-gated Na^+ channels that are concentrated at (or near, depending on the type of neuron) the **axon hillock**, the region where the bulky cell body funnels down into the long tube that is the axon. These channels are closed when the neuron is at rest (i.e., with a membrane potential of −70 mV). However, when the neuron has been sufficiently **depolarized** (e.g., the voltage raised to roughly −20 mV (again, this varies depending on cell type); see *Tip 2.6*), these channels open, and allow for the very rapid influx of Na^+ ions. Recall that this influx is propelled by both the electrical gradient and the chemical gradient that exists across the cell membrane. This influx of Na^+ ions gives rise to the action potential (or "spike" in neurophysiology vernacular), which is the basis for neuronal communication.

How neurons communicate: the action potential

A neuron initiates an action potential by taking advantage of the local depolarization produced by the influx of Na^+ ions that occurs at the axon hillock. It has to "act fast," because although this event produces a short-lived "cloud" of depolarization in the vicinity of the axon hillock, this "cloud" will quickly dissipate due to the rapid diffusion of Na^+ ions throughout the intracellular space (recall that there's a low concentration of Na^+ ions inside the cell). The neuron exploits this temporary depolarization by having another cluster of voltage-gated Na^+ channels that is "strategically" located just a little way along the axon. The channels of this cluster experience the brief pulse of depolarization from the hillock and they, in turn, open. Next, guess what? There's *another* cluster of voltage-gated Na^+ channels even further along the axon … . This pattern repeats, and in this way an action potential is propagated along the length of the axon until it reaches the dendrites of the next neuron. (You may be wondering, "But how did the initial depolarization that triggered the activity at the axon hillock come to pass?" Stick with me, and we'll come to that.)

When the action potential arrives in the vicinity of a dendrite from another neuron, it encounters a change in the morphology (i.e., shape) of the axon. This is a swelling of the axon into what is referred to as a synaptic bouton, or presynaptic terminal (*Figure 2.7*). For a neural signal to pass from one cell to another, there needs to be a synapse linking them. At the presynaptic terminal one finds the machinery necessary for converting the electrical signal of the action potential into the chemical signal that will be transmitted to the postsynaptic terminal. (Note from *Figure 2.7* that the pre- and postsynaptic cells do not touch, there is a gap (the **synaptic cleft**) between them.) That is, the electrical signal does *not* jump to the next neuron. Instead, the rapid depolarization triggered by the action potential opens voltage-gated calcium-ion (Ca^{++}) channels located in the membrane of the presynaptic terminal. Not unlike Na^+, Ca^{++} ions are in much higher concentration outside than inside the neuron, and thus the opening of voltage-gated Ca^{++} channels results in an influx of Ca^{++} ions into the presynaptic terminal. Ca^{++} ions have a special status in the nervous system, in that they can initiate many biochemical processes within the cell. At the presynaptic terminal, the influx of Ca^{++} ions triggers a cascade of events that results in the release of neurotransmitter into the synaptic cleft (*Figure 2.7*; see *Tip 2.7*). (Note that it is almost never the case that a neuron makes contact with just one other neuron. Rather, axons have multiple branches (in some cases thousands), each of which ends in a synaptic terminal. The action potential propagates equally along each branch.)

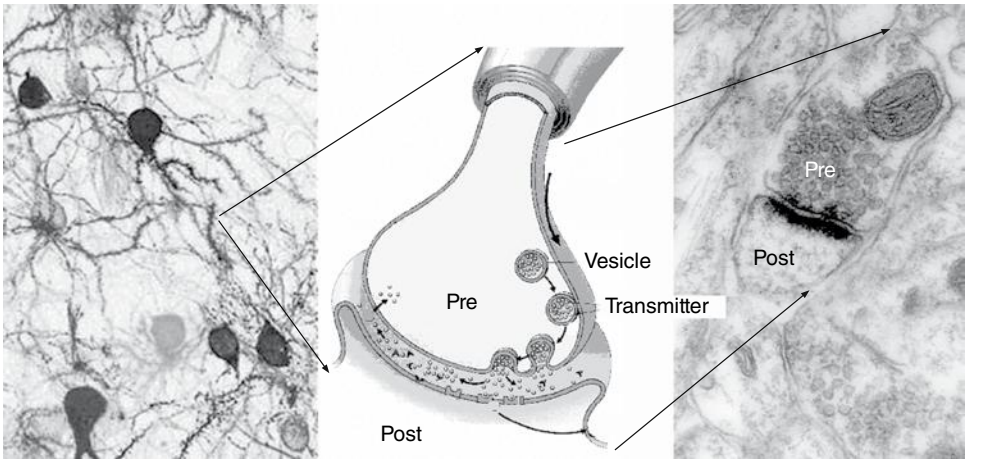

FIGURE 2.7 Left-side panel: light microscope image of neural tissue with cell bodies and processes visible. Many of the dendrites are studded with dendritic spines, including the one from which a tiny region is blown up to illustrate a synapse in the center panel. Center panel: diagram of a synapse, illustrating (with arrows) the events triggered by the arrival of an action potential: vesicles filled with neurotransmitter in the presynaptic terminal ("pre") are transported to the membrane, where they fuse with it to release neurotransmitter into the synaptic cleft; subsequently molecules of neurotransmitter (or, depending on the type of synapse, a catabolyte), are reuptaken back into the presynaptic terminal. Right-side panel: an electron microscope image of a synapse, with vesicles visible in the presynaptic terminal, and the "postsynaptic density," partly comprised of membrane-spanning receptors, visible as a dark band at the postsynaptic terminal. Source: Buszáki, 2006. Reproduced with permission of Oxford University Press, USA.

Tip 2.7

The electric-to-chemical-to-electric conversion is typical of most synapses in the CNS. However, some classes of neurons in the brain are "electrotonically coupled," and can pass current directly between themselves.

How neurons communicate: the postsynaptic consequences of neurotransmitter release

On the postsynaptic side of the synapse, the membrane is studded with *neurotransmitter receptors*, each of which can bind with a molecule of the just-released neurotransmitter. This, in turn, will, depending on the type of receptor, produce one of any number of possible effects in the postsynaptic neuron. The most straightforward of these to describe, and one that's satisfactory for our present purposes, is to open a **ligand**-gated Na^+ channel – that is, a molecule of neurotransmitter acts like a key by fitting into a special slot in the receptor and "unlocking" it. With its channel now open, the receptor allows the influx of Na^+ ions into the postsynaptic terminal of the dendrite (See *Thought Box 2.1*). Thus, in our example, the binding of a molecule of neurotransmitter to a receptor has the effect of generating a small "cloud" of depolarization in the vicinity of this receptor within the postsynaptic terminal. Now if only one such event happens, the cloud of depolarization quickly dissipates. If, however, many molecules of neurotransmitter have bound with many receptors, particularly if this has happened more-or-less simultaneously at many synapses (i.e., if this neuron is on the receiving end of a volley of many action potentials arriving simultaneously from many different presynaptic neurons) then all these individual pulses of depolarization may combine, via their summation, to the point at which the cell's membrane voltage is raised to the neighborhood of −20 mV, in which case an action potential may be triggered in this postsynaptic neuron. (A mechanism

THOUGHT BOX

2.1 How do membrane channels work?

The membrane-spanning channels of neurons are made up of complexes of proteins that span the membrane from intra- to extracellular space. The channel's walls are formed by several subunits, as is illustrated in *Figure 2.8*. A channel's specificity for one type of ion is determined by the physical size of its pore

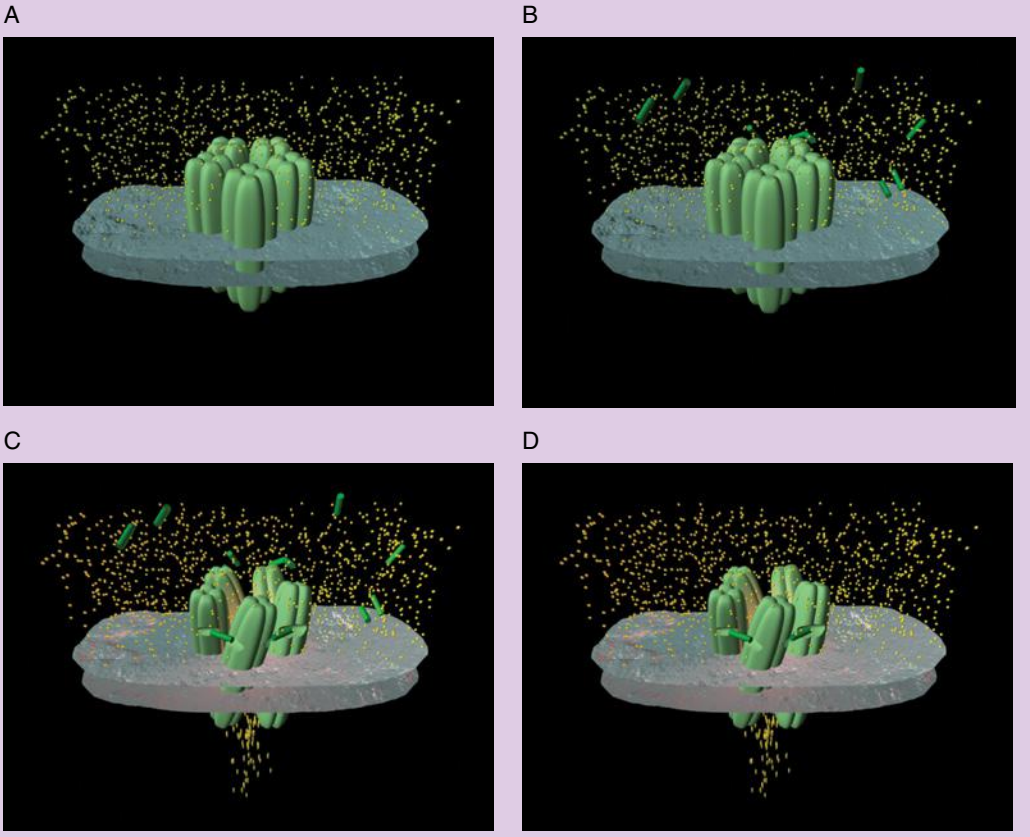

FIGURE 2.8 Four panels illustrating the effects of the neurotransmitter GABA binding with a membrane-spanning $GABA_A$ receptor (a subtype of GABA receptor). **A**. The receptor is composed of five separate proteins, each one consisting of four membrane-spanning domains (green "cigars"). As a functional unit, the receptor spans the neuronal membrane (gray planes), and provides a pathway for the inflow of ions (yellow dots represent a cloud Cl^- ions in the extracellular space). The receptor is shown in its resting, closed state, with no neurotransmitter bound, and no available path for ions to flow across the membrane. **B**. Shorter, darker green cylinders represent GABA molecules having been released into the synaptic cleft. (I.e., an action potential in a GABAergic (*Tip 2.11*) neuron has triggered the release of GABA from the presynaptic terminal (not shown) into the cleft.) **C**. Binding of GABA molecules at two binding sites results in conformational change of receptor proteins (illustrated here as a mechanical twisting of subunits) which opens the pore of the receptor, thereby allowing Cl^- ions to enter the neuron. **D**. For some period of time after unbound GABA has been cleared from the synapse, the receptor remains active. Source: Images courtesy of Mathew V. Jones, University of Wisconsin-Madison. Reproduced with permission.

Thought Box 2.1 *Continued*

(e.g., Na^+ channels are simply too small to allow large ions or molecules to pass through), as well as by the properties of binding sites located in the pore of some channels that result in the preferential permeability to some ions over others. When closed (i.e., "at rest"), the pore is too narrow for anything to pass through. When activated, the channel twists (due to a change in conformational state of one or more of the subunits), thereby enlarging the pore and allowing ions to pass through. Depending on the type of channel, activation is accomplished by the binding of a ligand to the binding site (as is the case with AMPA and GABA receptors), by a change of membrane voltage, or by activation of the channel via chemical signaling from within the cell. The latter is typical of many channels that are influenced by a neurotransmitter other than glutamate or GABA. In the case of the neurotransmitter dopamine, for example, the dopamine receptor is not part of a ligand-gated channel. Instead, the binding of dopamine to a receptor triggers a cascade of biochemical events inside the postsynaptic terminal, and a downstream consequence of this can be the opening of a membrane-spanning channel. Note that such a multi-step cascade is likely to take longer to influence the voltage of a neuron than is a ligand-gated channel. This is one of the reasons that neurotransmitters such as dopamine are considered to be neuromodulators – their effect is to modulate the responsivity of the neuron to the faster-acting, "driving" effects of glutamate and of GABA.

by which the action potentials from many neurons can be coordinated to all arrive at a postsynaptic neuron at the same time is considered near the end of this chapter, in the section *Synchronous oscillation*.)

Different neurotransmitters and different receptors can produce different effects on the postsynaptic cell

The postsynaptic effects of neurotransmission that were described in the previous paragraph apply to the **excitatory neurotransmitter** glutamate binding to a particular kind of glutamate receptor called the AMPA receptor (see *Tip 2.8*). There are other glutamate receptors in the brain that work differently, and we will consider them in some detail when we discuss memory functions. **Glutamate** is released by cortical pyramidal cells, and because these are the most numerous neurons found in the cortex, glutamate is the predominant excitatory neurotransmitter in the CNS. Equally important for the functioning of the brain is **inhibitory neurotransmission**, and this is most commonly carried out by the neurotransmitter **GABA** (see *Tip 2.9*). GABA is the primary neurotransmitter released by **inhibitory interneurons**, neurons whose primary function is to **hyperpolarize** neurons (i.e., to make their voltage more negative). The most common GABA receptor produces its hyperpolarizing effects by opening channels that pass chloride ions (Cl^-), and because the extracellular concentration of Cl^- ions is considerably higher than the intracellular concentration, opening these channels results in an influx of negatively charged Cl^- ions, and, thus, a negative shift in the membrane potential (*Figure 2.8*). The reason that this effect on the postsynaptic neuron is inhibitory is because it pulls the

Tip 2.8

Neurotransmitter receptors are often named after chemicals that can mimic the effects of their naturally occurring ligands. Thus, the *AMPA* receptor is named after the chemical that binds this type of glutamate receptor, but not other types of glutamate receptor: α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid.

Tip 2.9

GABA is the acronym for the molecule gamma-aminobutyric acid.

Tip 2.10

Positively charged ions, as a category, can be referred to as **cations**, negatively charged ions as **anions**. These terms are often used when describing ion channels that are not specific to one type of ion.

Tip 2.11

The suffix used to convert the names of many neurotransmitters from nouns to adjectives is "ergic." Thus, for example, a glutamate-releasing synapse is called "glutamatergic," a GABA-releasing neuron "GABAergic," and so on.

membrane voltage away from the trigger potential of −20 mV, thereby inhibiting the neuron's probability of firing an action potential (*Tip 2.10*).

Housekeeping in the synaptic cleft

Although the pre- and postsynaptic terminals of a synapse are very close together, there is no guarantee that any one molecule of neurotransmitter will bind with a receptor. Rather, binding is a probabilistic event, with the probability of binding influenced by many factors, including the amount of neurotransmitter released by an action potential, and the density of receptors in the postsynaptic membrane. It is also important to know that those molecules of neurotransmitter that do bind with a postsynaptic receptor do not enter the postsynaptic cell. Rather, after some period of time, they disengage from the receptor and float back into the synaptic cleft. The nervous system thus has to solve the problem of clearing out the synapse after each action potential, lest the lingering molecules of neurotransmitter in the synapse continue to influence the postsynaptic neuron for longer than intended. The nervous system has evolved many different solutions to this problem that are implemented at different synapses. Common to many is the process of **reuptake**, whereby molecules of neurotransmitter are taken back into the presynaptic terminal via specialized complexes of membrane-spanning proteins. Reuptake is an active process that requires energy, because it entails moving molecules of neurotransmitter from a low-concentration environment (the extracellular space) into a high-concentration environment (the presynaptic terminal). That is, it entails working against a chemical gradient (see *Thought Box 2.2*). At glutamate synapses, the reuptake occurs both at the presynaptic terminal and at astrocytes that are located adjacent to the synapse. (In astrocytes, glutamate is converted into a precursor metabolite, which is transferred back to the presynaptic pyramidal cell for conversion back into glutamate.) At GABA synapses, the neurotransmitter is reuptaken into the presynaptic terminal by the GABA transporter. At synapses for many of the neuromodulatory transmitters, there are enzymes that either break down the molecules of neurotransmitter into smaller, constituent molecules, or transform them into a different molecule, the result in either case being a product that can no longer bind with the postsynaptic receptors. These now-inert molecules are then taken back into the presynaptic neuron, where they are reconverted into molecules of neurotransmitter. There are entire textbooks devoted to the details of how neurotransmitters are synthesized and metabolized (often falling under the rubric of "neuropharmacology"), and others to the details of the trafficking, release, and reuptake of neurotransmitters at the presynaptic bouton. Although we won't devote much more verbiage in this book to the detailed workings of the synapse, the facts that we have covered up to this point are important for understanding two general properties that are highly relevant for cognitive neuroscience. One, introduced in *Thought Box 2.2*, is how the metabolic demands of the synapse trigger physiological signals that are the basis of neuroimaging signals that can be used to study the brain. The second, detailed in *Real-World Applications 2.2*, is that the synapse is the target of virtually every drug (whether medicinal or recreational) that affects cognitive functioning. (Finally, I recommend a visit to *Web Link 2.1*, which illustrates how an understanding of the neuron at this level of detail is being used by computer scientists to build more efficient computers, as well as more accurate computer simulations of the brain itself.)

THOUGHT BOX

2.2 The metabolic demands of the action potential and synaptic activity

The generation of an action potential entails reversing the electrical and chemical imbalances that are characteristic of the neuron at rest. How the neuron restores these imbalances turns out to be the basis for many neuroimaging techniques. One key mechanism is the so-called **Na^+/K^+ pump**, a membrane-spanning complex of proteins that act as a "reverse channel." At the cost of one molecule of adenosine triphosphate (ATP) per cycle, the Na^+/K^+ pump expels three Na^+ ions and draws in two K^+ ions. Also highly energy-demanding is the process of releasing molecules of neurotransmitter into the synaptic cleft (exocytosis). ATP, the "fuel" that is needed for these operations, is derived from the processing of glucose in mitochondria inside the neuron. Glucose, in turn, is delivered to cells via the blood stream. Herein lies the linkage to the signal that is measured by **functional magnetic resonance imaging (fMRI)** and some applications of positron emission tomography (PET), both to be discussed in more detail in *Chapter 6* and subsequent chapters), as well as by certain types of functional tissue imaging (*Chapter 3*): elevated activity in neurons creates a need for arterial blood, and the resultant increase of oxygenated blood, or of glucose, to active parts of the brain is what these methods detect. (The principle is the same for all tissues of the body. Think about whether more blood flows to the muscles of your arm when you are lifting something heavy, or when your arm is just hanging by your side.)

Interestingly, neurotransmitter reuptake, although a metabolically expensive process, isn't directly responsible for the consumption of ATP. Instead, it leverages electrochemical ion gradients across the membrane via a process called **cotransport**. A useful analogy is to consider a revolving door. To get it "inside," a molecule of neurotransmitter is yoked to a Na^+ ion. Now we have a situation in which the chemical gradients of the yoked components are in opposition – the low intracellular concentration of Na^+ provides an inward "pull," and the opposite is true for the neurotransmitter. It's as though two people have entered a door that's rotating counterclockwise (anticlockwise), and one (the "Na^+ ion") is pushing the door in the counterclockwise direction so as to enter, while the other (the "molecule of neurotransmitter") is pushing in the opposite way. (The role of the neurotransmitter can be played by a two-year-old in our analogy: *No, Mommy, I don't want to go into that store!*) The stalemate is broken by adding a third "person" who is inside and who wants to leave: cotransport also entails the simultaneous transport of a molecule of K^+ along its concentration gradient, from inside the cell to outside. "Two against one," the molecule of neurotransmitter "loses," and it ends up back inside the neuron.

If cotransport "passively" takes advantage of chemical gradients, why is it metabolically expensive? The answer is that although the reuptake process itself doesn't consume ATP, its operation decreases the resting-state imbalance of higher intracellular concentration of K^+ and higher extracellular concentration of Na^+. Thus, each cycle of the reuptake processes prompts a compensatory, energy-expending cycle of the Na^+/K^+ pump to in order to restore the imbalance.

REAL-WORLD APPLICATIONS

2.2 Most drugs that affect the brain have their effects at the synapse

Whether one considers pharmaceutical medications that are prescribed to treat psychological, psychiatric, or neurological disorders, or "recreational" drugs that people take to get high, the synapse is far and away the site of action of most neuroactive drugs. Many recreational drugs have their effects by mimicking endogenous ligands. Thus, for example, the active component of heroin mimics endogenous compounds called opioids and binds to opioid receptors. The active component of marijuana mimics endogenous compounds called cannabinoids and binds to cannabinoid receptors. Cocaine, in contrast, has its effect by blocking the reuptake of dopamine into the presynaptic terminal, thereby keeping molecules of dopamine in the synapse longer, and exaggerating the effect of dopamine release. Interestingly, the mechanism of the class of antidepressant medications known as selective serotonin reuptake inhibitors (SSRIs; examples include Prozac and Zoloft) work on the same principle, but on a different neurotransmitter system.

Some drugs don't directly gate receptors, but, instead, modulate their action. Benzodiazepines (such as diazepam (first marketed as Valium)), for example, bind to a site on the $GABA_A$ receptor, and have the effect of increasing its Cl^- conductance when GABA is released. (That is, benzodiazepines don't directly activate these receptors, but, when bound to the receptors, they potentiate of the effects of GABAergic neurotransmission. See *Figure 2.8*.)

Finally, many naturally occurring *neurotoxins* also do their work at the synapse. For example, curare is a toxin that indigenous peoples of Central and South American rain forests have learned to extract from the skin of brightly colored "poison dart frogs." Curare paralyzes its victims by blocking the release of the neurotransmitter acetylcholine (ACh) at the neuromuscular junction, the synapse at which nerve endings instruct muscle cells to contract. (Diabolically, curare has minimal effects on the CNS, and so paralyzed victims are presumably aware of their condition as the hunters close in … .)

One exception to this synaptocentric pattern is tetrodotoxin (TTX), the deadly poison administered by puffer fish, blue-ringed octopi, and many other sea creatures that one should avoid. Rather than working at the synapse, TTX interferes with the ability to generate action potentials by blocking the voltage-gated Na^+ channel.

Neuroanatomical techniques exploit the physiology of the neuron

Now that we have an understanding of some aspects of how the neuron "works," we can return to a topic from earlier in this chapter – the **laminar** organization of cortical connectivity – to consider how this knowledge has been acquired. Let's start by considering that no matter how long, or multiply branched, is an axon, it's part of one cell. Thus, there needs to be a mechanism, for example, for the transport of proteins that are synthesized from DNA in the nucleus of the neuron to synapses at far reaches of each axonal branch. (For me, the "gee whiz" factor is particularly high when I think of the giraffe, or of massive whales … .) And so, whereas our attention up to this point has been on various types of trans-membrane transport, intracellular mechanisms for **axonal transport** are critical for the healthy functioning of the neuron. The reason for bringing this up now is that, for centuries (whether they have known it or not), anatomists have taken advantage of axonal transport to explore connectivity in the brain (*Methodology Box 2.2*; *Figure 2.9*).

METHODOLOGY BOX

2.2 Cell biological methods for measuring neuronal connectivity

Axons are microscopically small. Although bundled tracts of thousands of axons can be visible to the naked eye (e.g., the optic nerve, tract, and radiations; *Figure 2.6*), this sheds no light on the destination of individual axons. One strategy for determining precisely where axons project to is to inject a substance into a region of the brain, let the natural processes of intracellular transport "do their thing" (i.e., transport the substance from the region of uptake to other parts of the neuron), and later look for where the substance has been transported. Over the past 100 years or so, sometimes through trial-and-error, sometimes as a result of sophisticated understanding of cell biology, anatomists have devised many ways to address different questions about neuroanatomy. For our purposes we can think of three categories of cell-based (as opposed to neuroimaging-based) neuroanatomy: anterograde transport; whole-cell staining; and retrograde transport.

Anterograde transport would be used, for example, to determine whether, and how, neurons from somatosensory area S1 project to somatosensory area S2. To do the experiment, one would inject tracer into S1, wait for a set period of time, then sacrifice the animal, slice the brain, process the tissue, and, finally, inspect the tissue under a microscope to observe where the tracer ended up. Such an experiment depends on several factors. First, the tracer needs to be taken up by the dendrites and/or cell bodies of the neurons of interest. Second, one needs to know the amount of time it takes for the tracer to be transported to the ends of the neuron. Third, there needs to be a reliable way to detect the tracer under a microscope. With regard to the passage of time, this becomes particularly important if the tracer can "jump" the synaptic cleft, and thereby be passed from one neuron to another. Exquisitely detailed studies have been performed with such tracers such that, when different animals are sacrificed at different times relative to the injection, the anatomist can determine the monosynaptic connectivity of a region, its disynaptic connectivity, and so on. With regard to detection, some tracers are visible in and of themselves, others require the tissue to be stained or otherwise prepared so as to make the tracer visible.

Whole-cell staining is just what it sounds like. A nice demonstration is seen in the left-hand panel of *Figure 2.7*. The trick with this method is to use a stain that is selective for a particular kind of cell. For example, we'll see in *Chapter 4* that to study the local architecture of pyramidal vs. interneurons in primary somatosensory cortex, the researchers take advantage of the fact that one class of interneurons contains the protein parvalbumin, but other interneurons and pyramidal cells do not.

Retrograde transport is the opposite of anterograde transport. It relies on a tracer that is taken up at the presynaptic terminal (perhaps by "hijacking" the cotransport mechanism), then carried "backwards" along the axon to the cell body and dendrites. *Figure 2.9* illustrates how this approach can be used to determine the laminar organization of projections from S1 to S2 vs. to the nuclei of the "somatosensory thalamus" (see *Tip 2.12*).

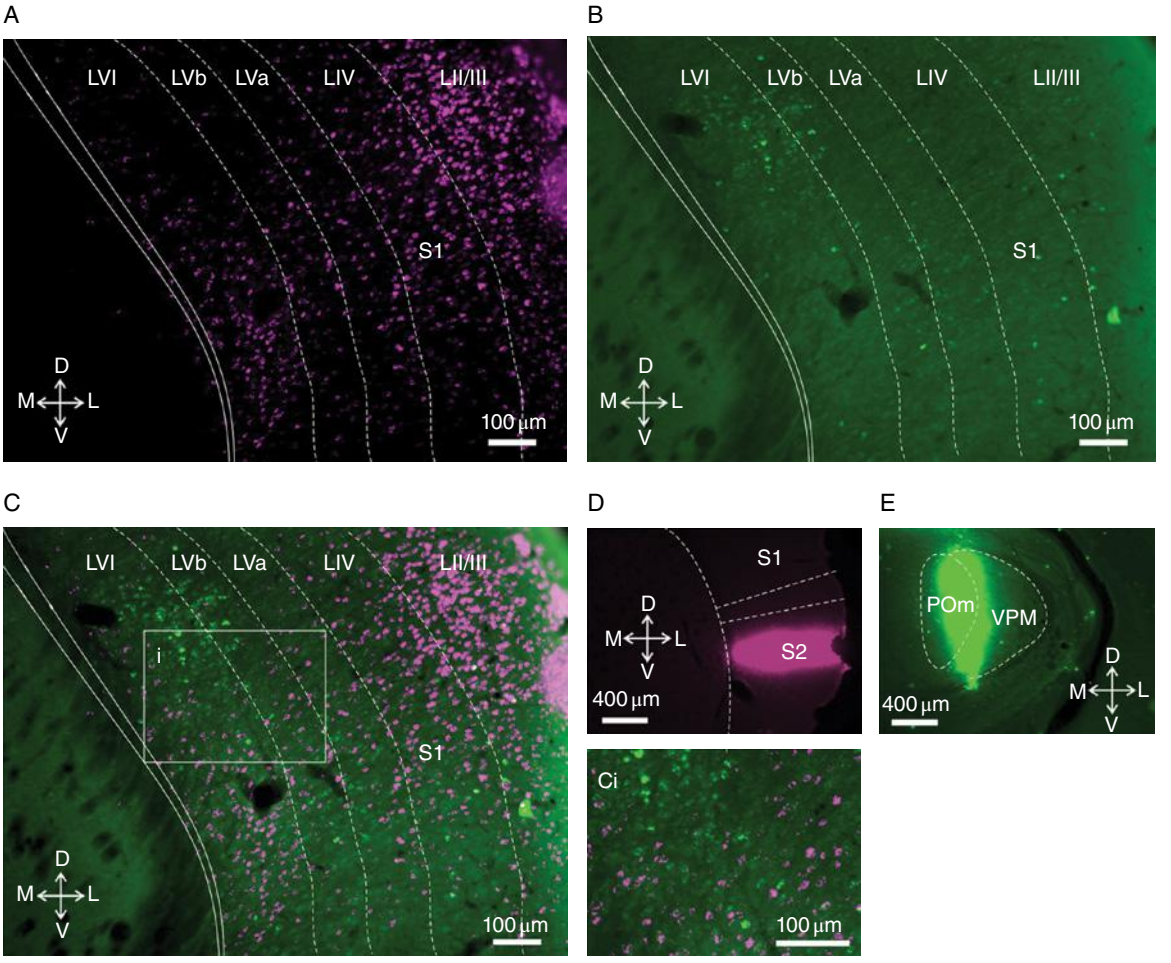

FIGURE 2.9 A neuroanatomical tracer study of the laminar organization of projections from primary somatosensory cortex (S1). To follow the logic of the experiment, look first at panel **D** – this shows the region of secondary somatosensory cortex (S2) where the (purple-colored) tracer was injected. It is a fluorescent, retrograde tracer called "Retrobeads." Panel **A** shows the distribution of labeling resulting from the injection shown in **D**. That is, the purple Retrobeads were taken up at presynaptic terminals in S2 (panel **D**) and retrogradely transported back to the cell bodies (panel **A**) of the neurons whose axons formed those presynaptic terminals (that is, of the neurons whose axons projected to S2). Note that the labeling is heaviest in layer II/III of S1, meaning that it is neurons in this layer that send the heaviest feedforward projection from S1 to S2. (Note, also, that this laminar organization is not absolute – biological systems are rarely as tidy and lawful as one might want them to be.) Next, let's go to panel **E**, which illustrates the injection site of green Retrobeads into the posterior medial nucleus (POm) and ventral posterior posterior medial (VPM) nucleus of the thalamus. The green spots concentrated in the upper left-hand corner of panel **B** are the retrograde labeling resulting from this thalamic injection. This indicates that the S1 neurons projecting to thalamus are located primarily in layers VI and Vb. Panel **C** illustrates an overlay of **A** and **B**, to emphasize the distinct projection profiles of the superficial vs. the deep layers of S1. Panel **Ci**, a blow-up of the box in panel **C**, shows the absence of "double-labeling," the presence of which would have meant that individual neurons project to both S2 and the thalamus. (Addressing this question was, in fact, the primary reason that this experiment was performed.) The key in the lower-left corner of each image indicates the dorsoventral and mediolateral axes. Source: Petrof, Viaene, and Sherman, 2012. Reproduced with permission of Wiley.

Tip 2.12

Note that I am deliberately choosing not to name various neuroanatomical tracers, because there are hundreds, and our purpose in this chapter is to convey an idea of how neuroanatomical connectivity is determined, not to teach the details of how one would perform such an experiment.

OSCILLATORY FLUCTUATIONS IN THE MEMBRANE POTENTIAL

Neurons are never truly "at rest"

As previously noted, the small cloud of depolarization produced by the opening of any single ligand-gated Na^+ channel typically won't, by itself, be enough to trigger an action potential, particularly when the channel is located on a distal dendritic branch, far from the cell body and its axon hillock. If this one channel were to periodically open then close, open then close, what one would observe at the cell membrane in the immediate vicinity of the receptor would be a slight depolarization – say, from −70 mV to −69 mV – followed by a return from −69 mV back to −70 mV, followed by another rise back to −69 mV, and so on. That is, the local membrane voltage would oscillate. Now, of course, we already know that the factors influencing the membrane voltage are much more complicated than the behavior of a single ligand-gated ion channel. For starters, a single synaptic event (i.e., an action potential in the presynaptic neuron) is likely to activate hundreds, if not thousands, of individual channels. These individual depolarizing events will add together (they will "summate"). So, too, will the depolarizing effects produced by activity at other synapses. As a result, the overall effect that is experienced by the synaptic membrane will depend on the synchrony of incoming action potentials from glutamate-releasing axons. That is, if many action potentials arrive at about the same time, the aggregated depolarizing effect will be much larger than if the same number of incoming action potentials are spread out in time, because the depolarizing effect of the earliest-arriving action potentials will have started to dissipate (also referred to as "decay") before the depolarizing effect of the later-arriving ones starts to kick in. A second factor that influences fluctuations in overall membrane potential is the hyperpolarizing effects of action potentials at GABAergic synapses. What emerges from this cacophony of thousands of events at individual channels, some depolarizing and some hyperpolarizing, is an ongoing pattern of fluctuations in the dendritic membrane potential that can be measured with an electrode in the extracellular space. Because the dendritic branches from many, many neurons are located in close proximity to each other, it is typically not possible to isolate the fluctuations attributable to a single neuron. Rather, what is recorded is the **local field potential (LFP)**, a reference to the fact that it's the local region of cortex where these dendrites are located (i.e., the "dendritic field") from which the signal is being measured (see *Methodology Box 2.3*; *Figure 2.10*; and *Web Clip 2.3*).

Despite the fact that there can be literally hundreds of thousands of individual channels distributed across the tens to hundreds of neurons contributing to the LFP recorded by any one electrode, the LFP is nonetheless often observed to fluctuate in an orderly oscillation. Indeed, different oscillatory frequencies, or "states," are so typical of the cortex that they've been given names. One common state is when the LFP oscillates with roughly 40 up–down cycles per second (i.e, 40 Hz); the range of oscillatory frequencies within which this falls, from roughly 30 Hz to roughly 80 Hz, is referred to as the **gamma frequency band** (or, "the gamma band," or, sometimes, in the shorthand slang of the laboratory, just "gamma"). (This and other frequency bands are illustrated in *Figure 4.3*.) How can the brain orchestrate what we've just referred to as a cacophony of individual single-channel events into a steady, predictable up-and-down rhythm? One important factor is that neurons are wired up in a way that facilitates the control of their oscillations. For many pyramidal cells, for example, inhibitory inputs from interneurons tend to synapse near the base of the dendrite, or even on the cell body itself. This positioning allows these inhibitory synapses to act as a kind of "gate" that either does or does not allow the depolarizing currents from more distally located glutamatergic synapses to

METHODOLOGY BOX

2.3 Extracellular recording: action potentials and LFPs

Although many methods have been devised to study the electrical properties of neurons, most have made use of some variant of the electrode. A microelectrode is a fine-tipped (on the order of one micron across) conductor of electricity, typically a glass micropipette filled with a conductive fluid or a platinum or tungsten wire, that can be inserted into brain tissue (thus, a "penetrating electrode"), and is connected to an amplifier. Because it is conductive, it detects the changes in voltage that have been detailed in much of this chapter. Many of the properties of the neuron that have been described in this chapter were discovered via **intracellular recordings** obtained with in vitro methods, in which individual neurons, or more often slices of CNS tissue, are surgically removed from an animal and kept alive "in a dish" by bathing it in artificial CSF. Only by recording intracellularly can one measure, for example, the activity of a single postsynaptic channel, or the kinetics of voltage-gated ion channels. However, because cognitive neuroscience, by definition, deals with the neural processes that underlie behaviors (that we associate with cognition), the emphasis in this book will be on **extracellular recordings** obtained in vivo – that is, recordings made outside of the cell in the brain of a living animal.

From outside the cell, there are two types of signal that one can measure: action potentials and LFPs. Because action potentials are all-or-none events – there's no such thing as a "big" or a "little" action potential – they are treated as binary events, and a standard way to quantify a neuron's activity is by its firing rate. A neuron typically has a baseline firing rate, maybe 5 "spikes per second" (i.e., 5 Hz) for a generic pyramidal cell. The neuron's involvement in a particular function, let's say visual perception, can then be assessed by determining whether this firing rate changes systematically with a systematic change in the environment, say, flashing a light in an area that the animal is looking at. Depending on the neuron, and on the state of the brain, a neuron involved in the perception of this flash of light might exhibit either an increase or a decrease from its baseline firing rate. Depending on the cell type, an activated neuron's firing rate can be anywhere from 15 Hz to upwards of 200 Hz.

To record the LFP, the electrode must be far enough away from any one cell body that its measurements are not dominated by the signal from that cell. Proper filtering of the signal removes the contribution from action potentials, leaving the local field potential – the aggregated fluctuation of dendritic membrane potentials from cells in the vicinity of the electrode (see *Figure 2.10* and *Web Clip 2.3*).

An alternative to recording electrical activity with penetrating electrodes is to use a grid of electrodes that is positioned on the surface of the cortex, a technique called **electrocorticography** (**ECoG** (pronounced "ee-cog") for short). Because ECoG electrodes lie on the surface of the cortex, they lack the spatial resolution that can be obtained with penetrating electrodes. Additionally, they can only measure field potentials. The unique knowledge gained with this method, however, is manifest in *Chapter 9* and *Chapter 18*.

influence the membrane voltage at the cell body. As we'll see in *Chapter 4*, the biophysical properties of one common type of inhibitory interneuron make it tend to oscillate in the gamma range. A second factor that leads to the orderly oscillation of membrane potentials is that many interneurons, in addition to sending axons to local pyramidal cells, are also "wired together" via axonal connections that they make with each other (i.e., they are reciprocally connected). As a result, the activity of these interneurons

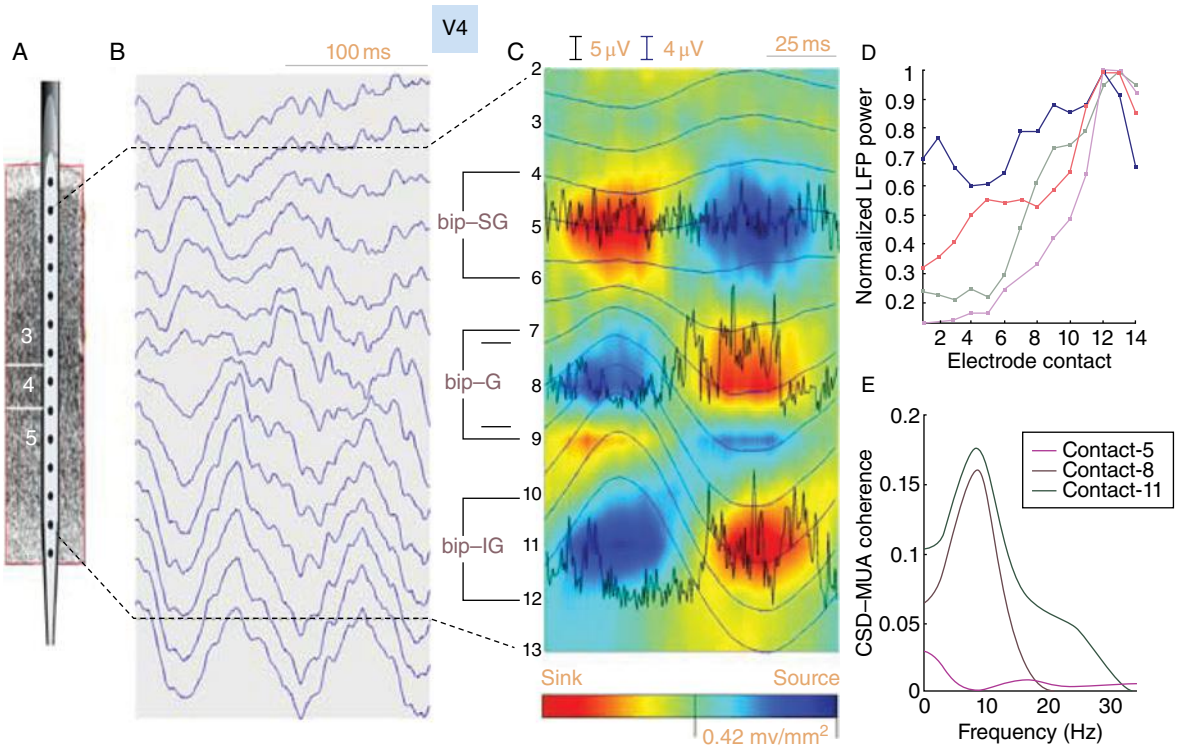

FIGURE 2.10 The local field potential (LFP). **A.** Schematic diagram showing an electrode with 14 equally spaced (200 μm) contacts ("3," "4," and "5" refer to layers of cortex). **B.** 200 ms of LFP recorded at each of these 14 contacts. **C.** A current source density map, computed from the pattern of LFPs in panel **B**. What this shows is the pattern, over time, of where in this cortical column current is flowing from intracellular space to extracellular space (a "source"), or from extracellular space to intracellular space (a "sink"). To compute the current source density map, bipolar recordings are needed, and "bip-SG" indicates the two contacts used to obtain these recordings in the supragranular layer, "bip-G" in the granular layer, and "bip-IG" in the infragranular layer. The jagged black traces show "multiunit activity" (MUA), a measure of voltage fluctuation due to the local firing of action potentials rather than to LFPs. The smooth blue lines are transformations of the raw LFP that we will disregard. These recordings were made in an area called "V4" (as referenced in *Figure 2.4*). (The experiment illustrated here is also discussed in *Web Clip 2.3*.) Source: Bollimunta, Chen, Schroeder, and Ding, 2008. Reproduced with permission of the authors.

tends to be synchronized. The consequence for pyramidal neurons is that they tend to experience a regular pattern of the delivery, then dispersion, of hyperpolarizing currents.

Synchronous oscillation

A consequence of receiving a synchronized delivery of hyperpolarizing GABA 40 times per second is that the membrane potential of a pyramidal cell won't actually remain at the steady −70 mV that was implied at the beginning of this chapter. Rather, it will oscillate between, say, −90 mV and −50 mV. And because a neuron is much more likely to reach its firing threshold when its membrane potential is in the neighborhood of −50 mV than that of −90 mV, this results in a state in which the pyramidal neuron has, in effect, 40 "windows" per second during which it might be able to fire an action potential. Given this state of affairs, if a pyramidal neuron in area X wants to make a pyramidal

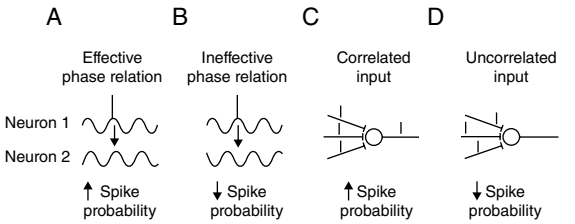

FIGURE 2.11 Illustration of how phase synchrony may govern the effectiveness of neural communication between a hypothetical "area 1" sending projections to a hypothetical "area 2." Panels **A** and **B** illustrate synchrony between an upstream and a downstream neuron. In **A**, neuron 1 and neuron 2 are oscillating with a phase lag of near 0 (i.e., membrane voltage of neuron 1 reaches the maximum depolarization point of its cycle just a fraction of a second more quickly than does neuron 2). A consequence of this is that an action potential fired by neuron 1 (illustrated by "spike") arrives at neuron 2 (illustrated by arrow) just as neuron 2 is at its maximally depolarized state, and thus the neuron 1 action potential has a relatively high probability of triggering an action potential in neuron 2. In panel **B**, neurons 1 and 2 are nearly 180 degrees out of phase (i.e., membrane voltage of neuron 1 reaches the maximal *de*polarization point of its cycle just a fraction of a second before neuron 2 reaches the maximal *hyper*polarization point of its cycle). Thus, an action potential fired by neuron 1 arrives at neuron 2 just as neuron 2 is at its maximally hyperpolarized state, and thus the neuron 1 action potential has a relatively low probability of triggering an action potential in neuron 2. Panels **C** and **D** illustrate synchrony between several neurons in one region ("region 1") that all project to a second region ("region 2"). In panel **C**, several upstream neurons are oscillating in phase with each other. Because the membrane potentials of neurons 1.A., 1.B., and 1.C. reach their maximally depolarized state at the same time, they are likely to fire action potentials at the same time. One consequence of this is that downstream neuron 2, to which 1.A., 1.B., and 1.C. all project, receives multiple depolarizing inputs all at the same time (illustrated by three "spikes" at same distance along three dendritic branches), and the summation of these inputs depolarizes neuron 2 to the point that it fires an action potential. In panel **D**, neurons 1.A., 1.B., and 1.C. are oscillating out of phase with each other, which means that their action potentials are not synchronized but, instead, randomly spread across time. The consequence for neuron 2 is that it receives depolarizing inputs that are staggered in time (illustrated by "spikes" at varying distances along three dendrites), and so there is little summation of inputs, thereby decreasing the likelihood that activity in region 1 will trigger an action potential in region 2. Source: Saalmann and Kastner, 2009. Reproduced with permission of Elsevier.

neuron in area Y fire an action potential, there are two things that it needs to do. First, it needs to time the delivery of its own action potential so that this action potential arrives during a depolarized phase of the membrane oscillation of neuron Y. Second, it needs many of its neighbors in area X to also send their action potentials at the same time, such that the area Y neuron receives many depolarizing impulses all at the same time. From this it is apparent that the synchronization of membrane oscillations in different populations of neurons is a critical factor in the smooth operation of the brain. Within a local group of cells, there's a degree of synchrony between interneurons and pyramidal neurons. Across regions, oscillatory synchronization of **ensembles** of neurons is necessary if they are to effectively communicate. Indeed, in many contemporary models of neuronal function, synchrony plays a critical role.

To illustrate how synchrony might be important for brain function, let's walk through a hypothetical example. Let's pretend that, while you're walking through the woods, three things happen simultaneously: (a) the sun breaks through the clouds; (b) a bird in an overhead tree takes flight; and (c) a bear comes ambling along the path in your direction. Now, because individual elements in your brain don't "know" that one of these events has more immediate relevance to you, the organism, than the other two, information about all three is propagated from the visual system to "downstream" brain systems that might implement one of three behaviors: (a) stopping to enjoy the warm caress of the sun; (b) reaching for the binoculars to watch the bird in flight; or (c)

RUNNING AWAY(!). According to synchrony models, one way that the nervous system has evolved to let choice (c) be the "winner" is that action potentials carrying information about the bear are timed to arrive during a depolarized phase in the oscillation of their downstream target system, whereas action potentials carrying information about the sun and about the bird arrive during a hyperpolarized phase of their downstream targets. Thus, the information about the bear is more potent, in a neural sense, and it thereby "wins" the "competition" to control your behavior. Such coordination and control of the LFP in different regions is referred to as **phase synchronization** (*Figure 2.11*). We shall see in subsequent chapters that some psychiatric disorders might be attributable to abnormal control of synchronization between neural systems.

It should be noted that whereas no neuroscientist questions the existence of oscillations in membrane potentials and in the LFP, there is vigorous debate about the extent to which these oscillations actually play a functional role in the workings of the brain. From one perspective, these oscillations could be nothing more than byproducts of the complex pattern of synaptic events experienced constantly by every neuron in the brain. This perspective might be paraphrased as *They happen, yes, but they may not actually serve any useful function*. On the other hand, with each passing month, it seems that there are new discoveries of specific neural systems (sometimes in the visual system (*Chapter 3*), sometimes in the systems that govern motor control (*Chapter 7*), sometimes in the hippocampus (*Chapter 10*)) whose functioning seems to depend on the precise synchronization of oscillations in different ensembles of neurons. Keeping this controversy in mind, the phenomenon of neuronal oscillations is one that we will return to at several points in this book.

COMPLICATED, AND COMPLEX

The human brain is a truly an amazing thing. It is made up of billions of neurons and trillions of synapses. What we have considered in this chapter only scratches the surface of all there is to know about the brain's molecular and cellular makeup. Entire careers have been, and will continue to be, devoted to understanding these elemental components of the brain. With the facts that we have considered, and the questions we have posed, however, we have enough foundational knowledge that we can now get on to what this book is about: cognition. While all these facts about how the brain is put together and how it works are still fresh in the mind, however, it is worthwhile considering a distinction made very eloquently by György Buszsáki in his 2006 book *Rhythms of the Brain*. The nuts-and-bolts facts of how cells in the brain work are, indeed, *complicated*. How this all works together to give rise to cognition, however, is not only complicated, it's *complex*. "The term 'complex' does not simply mean complicated but implies a nonlinear relationship between constituent components," and refers to properties often termed "spontaneous, endogenous, … self-organized, self-generated, self-assembled, and emergent" (p. 11). Stated another way, what we shall see again and again in our exploration of cognitive neuroscience is that "the whole is greater than the sum of its parts" (see *Thought Box 1.2*). This chapter has introduced many of the critical "parts" – parts of the brain, neurons, and neurotransmitters – as well as some of their properties – ion channels, oscillating membrane potentials, action potentials, and oscillating LFPs. Now we can start to explore how these combine and interact to produce the wonder that is cognition. And we'll start with visual perception.

END-OF-CHAPTER QUESTIONS

1. In what ways do the anatomical organization of the adult brain follow from its developmental origin as the neural tube?
2. What factors explain the "crumpled up" shape of the brain? What evolutionary pressures may have produced this shape?
3. What is a distinctive property of each layer of neocortex? Why might there be some advantages to segregating these properties/functions by layer?
4. What are the principal disequilibria of the neuron that were emphasized in this chapter, and what role do they play in the generation of the action potential?

5. How are the disequilibria raised in question 4 maintained by the neuron? In what way does your answer to this question relate to physiological signals that are detected with fMRI and some types of functional tissue imaging?

6. It can be said that neurons communicate via signals that, at one level of analysis can be considered digital, yet from another level of analysis can be considered analog. What phenomena that were discussed in this chapter are an example of each?

7. What explains the oscillation of voltage across the cell membrane? What explains the oscillation of voltage in the LFP? How are these two types of oscillation measured?

8. Although some scientists have argued that neuronal oscillations are primarily byproducts of the workings of neurons and networks of neurons (i.e., that they may be "epiphenomenal"), there is a growing consensus that they may play an important role in governing the effectiveness of communication between one brain area and another. Describe the concept of phase synchronization, and the role it may play in neuronal communication.

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If there's only one book that this textbook inspires you to read, this might be it. Provides a rigorous neurophysiological and anatomical basis for much of the dynamical systems-influenced content of this book, including, for example, the final section of this chapter.

Diamond, Marian C., Arnold B. Scheibel, and Lawrence M. Elson. 1985. *The Human Brain Coloring Book*. New York: Harper Perennial.

In science, it's often said that "the best way to ensure that you understand a topic is to teach a class about it." The same might be said about neuroanatomy and drawing.

Morrison, John H., and Mark G. Baxter. 2012. "The Ageing Cortical Synapse: Hallmarks and Implications of Cognitive Decline." *Nature Reviews Neuroscience* 13 (4): 240–250. doi: 10.1038/nrn3200.

In Chapter 14 *we'll learn that the prefrontal cortex is one of the first regions of the brain to show age-related decline in healthy, middle-aged individuals. This paper shows that, in the monkey, this decline is largely due to a dramatic loss of dendritic spines in layer III, the cortical layer whose integrity is most closely tied to age-related cognitive impairment.*

Oztas, Emin. 2003. "Neuronal Tracing." *Neuroanatomy* 2: 2–5. http://www.neuroanatomy.org/2003/002_005.pdf.

A very concise overview of some of the physiology, and biochemistry, underlying anatomical tracing techniques.

Wandell, Brian A., and Jonathan Winawer. 2011. "Imaging Retinotopic Maps in the Human Brain." *Vision Research* 51(7): 718–737. doi: 10.1016/j.visres.2010.08.004.

Nice treatment of the use of MRI for tractography. Additionally, some of the content of this paper, particularly in the section on "Functional specialization and maps," will be relevant in subsequent chapters, particularly Chapter 9.