Chapter 6

From Neuronal to Hemodynamic Activity

In the previous chapters, we explained how the principles of magnetic resonance can be used to create images of the brain. We have further shown that by changing how electromagnetic pulses and gradient magnetic fields are applied, we can create MR images that have contrast based on any number of different biophysical properties, including proton density, relaxation constants like $T_1$ or $T_2^*$, diffusion, or perfusion. However, another step is necessary for MRI to become fMRI. We must identify a biophysical property—some quantity that is altered by information processing—that can be used as a marker of brain function.

Because information processing results from the activity of assemblages of neurons, some neuroscience techniques directly measure neuronal activity. Invasive electrophysiological methods like single-unit recording measure the changes in membrane potential and ionic currents caused by the transfer of information by neurons. However, to make a whole-brain image of neuronal activity using electrophysiological methods, one would need to have closely spaced electrodes placed throughout the brain—a prospect that is neither practical nor ethical in humans. Electroencephalography (EEG) and magnetoencephalography (MEG) measure neuronal activity using sensors located outside of the brain, and thus these non-invasive techniques can be used in humans, but even these valuable approaches have many limitations, especially in their spatial resolution. Some optical imaging techniques measure neuronal activity using voltage-sensitive dyes that change their transmissive properties in response to changes in neuronal membrane potential, potentially within milliseconds of neuronal activity. However, the invasiveness of deep-tissue optical measurements and the toxicity of the dyes used preclude this approach for the study of the intact human brain.

How does fMRI create images of neuronal activity? The short answer is that it does not! Instead, fMRI creates images of physiological changes that are correlated with neuronal activity. To presage the key concepts: the information-processing activity of neurons increases their metabolic requirements. The vascular system provides energy to meet these requirements in the form of two fuel sources, glucose and oxygen, the latter bound to hemoglobin molecules. And, because deoxygenated hemoglobin has magnetic properties that distort
Figure 6.1 An overview of the physiological changes leading to fMRI data. In fMRI studies, researchers draw conclusions about sensory, motor, and cognitive processes based on changes in the MR signal within specific parts of the brain. Yet, many links intervene between these mental processes and the measured data. These processes are realized through signaling and integration within groups of neurons, and this neuronal activity requires energy in the form of adenosine triphosphate, or ATP. Because the brain does not store energy, it must create ATP through the oxidation of glucose. Both oxygen and glucose are supplied through increased blood flow to active neurons. The increase in blood flow replaces deoxyhemoglobin in the capillaries, venules, and small veins of the active area with oxygenated hemoglobin. Since deoxyhemoglobin molecules have magnetic field gradients that alter the spins of nearby diffusing hydrogen nuclei, the presence of deoxyhemoglobin reduces their MR signal intensity. By displacing deoxyhemoglobin with oxygenated hemoglobin, the increase in blood flow results in a local increase in the MR signal.

Blood-oxygenation-level dependent (BOLD) contrast The difference in signal on T2*-weighted images as a function of the amount of deoxygenated hemoglobin.

Hemodynamic Having to do with changes in blood flow or other blood properties.

Neuron A cell that is the basic information-processing unit of the nervous system.

cortex (neocortex) The thin wrapping of cell bodies around the outer surface of the brain.

Soma The body of the cell; it contains cytoplasm, the cell nucleus, and organelles.

dendrite A neuronal process that receives signals from other cells, performing a primarily integrative function.

Axon A neuronal process that transmits an electrical impulse from the cell body to the synapse, performing a primarily signaling function.

Some types of MR images, changes in its concentration provide a measure of brain function based on blood-oxygenation-level dependent (BOLD) contrast.

It is important to recognize that BOLD contrast is a consequence of a series of indirect effects. It is a measure of changes in the magnetic properties of water molecules, which in turn reflect changes in the concentration of paramagnetic deoxyhemoglobin. The deoxyhemoglobin concentration is a physiological indicator of oxygen consumption, which reflects changes in neuronal activity evoked by sensory, motor, and/or cognitive processes (Figure 6.1). Through investigation of this chain of processes, a number of important questions have arisen. How direct is the link between neuronal activity and the BOLD signal? How well is the spatial distribution of neuronal activity reflected in the spatial distribution of blood flow? How well does the relative timing of vascular, or hemodynamic, events reflect neuronal activity in different groups of neurons comprising a functional network? Understanding the answers to these questions is critical to being an informed user of fMRI methods and an informed consumer of fMRI results. In this chapter and the next, we consider the links between neuronal activity, energy consumption, cerebral metabolism, blood flow, and the MR signal.

Neuronal Activity

We begin this inquiry with the neuron (Figure 6.2), which is the basic information-processing unit of the central nervous system. We will focus on the relationship between information processing in the neuron and the resulting energy requirements. Modern stereological evidence has estimated that the human brain contains about 100 billion neurons. Of these, about 20 billion are contained within the cortex, or neocortex, a thin wrapping of cell bodies around the outer surface of the brain. Each cell body, or soma, of a neuron, as in other cells of the body, contains cytoplasm, organelles such as the Golgi apparatus and mitochondria, and a nucleus containing DNA. In a typical neuron, the cell body gives rise to branching protoplasmic processes called dendrites that vary greatly in number and spatial extent. Neurons also usually have one or more protoplasmic processes called axons that transmit information to other neurons, via projections to their dendrites and cell bodies.
Neurons come in many varieties, some with dense dendritic arbors and some without any dendrites. Some neurons have long axons that travel great distances in the nervous system, others have short axons that terminate locally, and still others have no axons at all. In addition to neurons, the human brain contains other types of supporting cells, known as glial cells (glia), including astrocytes, oligodendrocytes, and microglial cells. Glial cells are not thought to be directly involved in information processing within the brain, but they do participate indirectly by helping with synapse formation and regulation of the chemical environment surrounding neurons.

A useful generalization is that neuronal activity can be characterized as either integrative or signaling. Integrative activity collects inputs from other neurons through connections on both the dendrites and the cell body. Signaling activity transmits the outcome of integrative processes to other neurons. The transfer of information between neurons occurs at specialized junctions called synapses, where an axon terminal process from one neuron (i.e., the presynaptic terminal) is located adjacent to the postsynaptic membrane of the dendrite or soma of another neuron. In most synapses, the presynaptic and postsynaptic elements are separated by a small gap, the synaptic cleft, in which chemicals released from the presynaptic element influence activity in the postsynaptic membrane. In a relatively small number of specialized synapses, the presynaptic and postsynaptic membranes are in physical contact and electrically connected.

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**Figure 6.2** The neuron. Neurons are organized into three basic parts. Dendrites integrate signals coming from other neurons via small gaps known as synapses. The soma, or cell body, of the neuron contains the nucleus and organelles that support metabolic and structural properties of the neuron. Changes in the membrane potential of the neuron are signaled to other neurons by action potentials that travel along its axon.

glial cells (glia) Brain cells that support the activities of neurons but are not primarily involved with information transmission.
integrative activity The collection of inputs from other neurons through dendritic or somatic connections.
signaling activity The transmission of the outcome of an integrative process from one neuron to another.
synapse A junction between neurons where the presynaptic process of an axon is apposed to the postsynaptic process of a dendrite or cell body.
synaptic cleft A gap between presynaptic and postsynaptic membranes.
concentration gradient A difference in the density of a substance across space. Substances diffuse along concentration gradients from areas of high concentration to areas of low concentration.

ion A charged atom.

ion channel A pore in the membrane of a cell that allows passage of particular ions under certain conditions.

pump A transport system that moves ions across a cell membrane against their concentration gradients.

sodium–potassium pump A transport system that removes three sodium ions from within a cell while bringing two potassium ions into the cell.

cellular signaling events cross the membranes without intervening chemical messengers. A neuron may have hundreds or even thousands of synapses on its dendrites and soma, and it has been estimated that there are 100 trillion synapses in the human brain.

**Ion channels in neurons**

Both neuronal integration and signaling depend on the properties of neuronal membranes, which are lipid bilayers that separate the internal contents of the neuron from the external milieu. An important role of neuronal membranes is to restrict the flow of chemical substances into and out of the neurons. When substances are allowed to diffuse freely, they tend to diffuse from areas of high concentration to areas of low concentration. That is, they move along a concentration gradient until equilibrium is reached. However, neuronal membranes prevent free diffusion. They do, however, have embedded proteins that form pores or channels through which some ions, such as sodium (Na⁺), chloride (Cl⁻), potassium (K⁺), and calcium (Ca²⁺), can diffuse (Figure 6.3). (Note that an ion is an atom that has either a negative charge from having gained one or more electrons, or a positive charge from having lost one or more electrons.) These ion channels are selective, such that some ions can pass and others cannot. Furthermore, channels have gating mechanisms that can close or open them to ion traffic. While some gating mechanisms depend on the actions of specific molecules, others are also voltage-dependent and open when the electrical potential difference across the membrane has reached a particular threshold.

While an open channel can allow ions to diffuse passively down their concentration gradients, membranes also contain transporters, or pumps, that can move ions across the membrane against their concentration gradients and thereby create or maintain an unequal distribution of some ions (see Figure 6.3). One of the most important pumps is the sodium–potassium pump. The sodium–potassium pump uses a transporter molecule that forces three sodium ions (Na⁺) out of the cell and then picks up and brings two potassium ions (K⁺) into the cell on the return trip. Due to the action of the sodium–potassium pump and other transporters, along with the selective permeability of the membrane channels to different ions, a neuron at rest has a greater concentration of K⁺ inside its membrane and a greater concentration of Na⁺, Ca²⁺, and Cl⁻ outside its membrane. Any transient change in the permeability of the membrane

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**Figure 6.3** Ion channels and pumps. Ion channels allow particular ions to diffuse across membranes along concentration gradients. They may be opened by the actions of particular molecules, or they may open when the voltage difference across the membrane reaches a threshold. Pumps move ions across membranes against their concentration gradients, usually at a cost of energy supplied by ATP. A very important pump transports sodium out of the cell while bringing potassium into the cell.
will cause an influx (movement into the cell) or an efflux (movement out of the cell) of these ions as the system attempts to eliminate the concentration gradient and establish equilibrium.

The diffusion of substances through channels down their concentration gradients requires only kinetic energy from heat, but the operation of pumps requires cellular sources of energy. For example, one turn of the sodium–potassium pump requires the energy of one molecule of adenosine triphosphate, or ATP, which is converted to adenosine diphosphate, or ADP. (We will have more to say about ATP later in this chapter in the section on cerebral metabolism.) Consider the analogy of a water tower where holes in the bottom of the water reservoir allow passage of the water into descending pipes below. Here the gravity gradient is analogous to the concentration gradient and the holes are analogous to open ion channels. The water will move through the holes and run through the pipes down the gravity gradient without additional energy. The situation is quite different, however, if we want to return the escaping water to the water tower. Active pumping against the gravity gradient is now required, and the pump requires energy to operate. Note that while this analogy is instructive, it is incomplete with respect to ions. Because ions have electrical charge, their unequal distribution also results in an electrical potential (about −40 to −70 mV) between the inside and outside of the membrane. Thus, the movement of ions across a membrane is governed by both chemical and electrical gradients.

**Neurotransmitters and action potentials**

The primary location for communication between neurons is the synapse (Figure 6.4). The presynaptic process of the axon releases neurotransmitters, which are chemicals that diffuse across the synaptic cleft and interact with receptors on the postsynaptic membrane that gate (i.e. control the opening and closing of) ion channels. For example, the neurotransmitter glutamate opens normally blocked ion channels that allow Na⁺ to move down its concentration gradient and through the postsynaptic membrane into the target neuron. This influx of Na⁺ ions decreases the electrical potential between the inside and outside of the membrane at the channel location. Another type of glutamate receptor called the NMDA (N-methyl-D-aspartate) receptor admits Ca²⁺ through its channel when a threshold membrane potential is reached. This local depolarization of the postsynaptic cell membrane is referred to as an excitatory postsynaptic potential, or EPSP, and thus glutamate is known as an excitatory neurotransmitter. Glutamate is the most common excitatory neurotransmitter in the brain, and it is released by about 90% of all neurons.

Other neurotransmitters, such as γ-aminobutyric acid (GABA), interact with other receptors to open chloride or potassium channels. Either the influx of the negatively charged Cl⁻ into the neuron or the efflux of the positively charged K⁺ out of the neuron results in a net increase in the resting potential in the vicinity of these newly opened channels. This local hyperpolarization of the neuronal membrane is referred to as an inhibitory postsynaptic potential, or IPSP, and thus GABA is known as an inhibitory neurotransmitter.

A single EPSP or IPSP is a transitory event. Afterward, the neurotransmitter will be deactivated or removed from the synaptic cleft and from the receptor, the channel that was opened by the neurotransmitter will close, and ion pumps will restore both the unequal distribution of ions across the membrane and the resting membrane potential. However, because a neuron may have thousands of synapses, it may experience a barrage of individual EPSPs and IPSPs simultaneously progressing throughout its dendritic trees and soma.
Figure 6.4 Synapses and the release of neurotransmitters.

axon hillock A region of the cell body located at the emergence of the axon. Changes in its electrical potential lead to the generation of action potentials.

These depolarizing and hyperpolarizing membrane potentials are integrated by the neuron. Both their timing and spatial pattern influence the net polarization of a specialized region of the soma called the axon hillock, which is located where the axon emerges from the cell body.
If, over a brief time interval, the net depolarization experienced at the axon hillock (i.e., the sum of the depolarizing signals minus the sum of the hyperpolarizing signals) decreases below a threshold voltage, large numbers of voltage-gated sodium channels will open and there will be a concomitant large influx of Na\(^+\) into the cell. This large depolarization spreads down the axon, opening more voltage-gated sodium channels farther and farther down the membrane. The wave of depolarization, known as a nerve impulse or action potential, sweeps down the axon in a self-propagating manner, independently of the EPSPs that triggered it. Eventually, the nerve impulse will reach the end of the axon, where a presynaptic terminal forms a synapse with another neuron. Here the wave of depolarization will open voltage-dependent channels in the presynaptic membrane that allow Ca\(^{2+}\) influx into the presynaptic terminal. This influx of Ca\(^{2+}\) initiates a cascade of events that causes the release of neurotransmitters into the synaptic cleft, which interact with receptors that gate postsynaptic ion channels on the target neuron. This initiates either an IPSP or EPSP on the postsynaptic membrane of the target neuron, thus propagating the signal to another neuron elsewhere in the brain.

One can think of information processing by neurons as the combination of their integrative and signaling roles. Integration reflects the total spatiotemporal pattern of EPSPs and IPSPs, each generated at a synapse from another cell, which collectively determines the relative polarization of the neuron. Note that only EPSPs can trigger action potentials. Hyperpolarizing IPSPs, in contrast, make action potentials less likely by making the membrane potential more negative. An EPSP that might have sufficient strength to depolarize the axon hillock below threshold when this region is at its normal resting potential may not be able to do so if the axon hillock was hyperpolarized by a preceding IPSP. Signaling reflects the binary output—that is, whether or not an action potential was generated—of the integration process within a neuron.

Neither form of information processing, whether postsynaptic or action potential, itself requires an external source of energy, because the associated movements of ions are along concentration gradients. However, both sorts of potentials cause changes in ion concentration that require energy to restore. For example, the influx of Na\(^+\) during an action potential causes a change in the local membrane potential of the neuron, so electrical gradients now oppose the reentry of the positively charged K\(^+\) into the cell. To restore the asymmetric distribution of Na\(^+\) and K\(^+\) across the cell membrane and return the membrane to its resting potential, the sodium–potassium pump removes three Na\(^+\) ions from within the cell for every two K\(^+\) ions it brings into the cell. The energy necessary for restoring these potentials, so that the neuron becomes ready for its next contribution to information processing, is discussed in the next section.

**Cerebral Metabolism:**

**Neuronal Energy Consumption**

Why are the energy demands of neurons important for fMRI? To help answer this question, imagine that neurons stored energy to buffer moderate changes in their neuronal firing rates. Could we then construct meaningful theories of brain function based on energy delivery by the blood supply? Or imagine that it were known that energy consumption following neuronal firing served to increase the synthesis of protein, in support of structural changes in the neurons initiated by learning. How would this change the interpretation of neuroimaging results? Finally, imagine that we learned (as was once thought true) that information processing accounted for a tiny fraction of the brain’s energy
budget. How then would one account for the enormous metabolic demands of the active brain?

Thought Question

Assume that the brain did indeed have large local stores of energy that could support neuronal activity. Based on what you know so far, would fMRI be possible?

We now know that these hypothetical situations are not true. Local brain regions require external sources of energy to support metabolic processes, and much of this energy facilitates the restoration of concentration gradients following changes in membrane potential. Thus, measurements of brain metabolism can be used to make inferences about brain activity. So although our interests as neuroscientists may be in the relationships between mind and brain (where in this context “brain” refers to the activity of neurons), we can draw inferences about brain activity by measuring its energy supply. Here, we delve more deeply into the energy needs of neurons and how those needs are met by the vascular system.

Adenosine triphosphate (ATP)

The principal energy currency for cells in the human body is adenosine triphosphate, or ATP. ATP is a nucleotide that contains three phosphate groups. Free energy is released when the third phosphate group of ATP is removed by the insertion of a water molecule, in a reaction called hydrolysis. In body tissues, ATP can be produced from many substrates, including the sugar glucose, fatty acids, ketone bodies, and even proteins. Glucose is stored throughout the body in the form of glycogen. However, there is little glycogen in the brain, and thus, to maintain function, the brain requires a continuous supply of glucose and oxygen via the vascular system. Under normal circumstances, the brain extracts about 10% of the approximately 90 mg/dL of glucose in arterial blood. If the glucose concentration in blood falls below about 30 mg/dL, a coma may ensue.

The generation of ATP from glucose has three primary steps: glycolysis, the TCA cycle, and the electron transport chain (Figure 6.5). Glucose transporter molecules move glucose through the interstitial space from capillaries to neurons. Once in the cytoplasm of brain cells, glucose is broken down through a reaction called glycolysis, in which the six-carbon glucose is cleaved into two three-carbon sugars, which are then catabolized through a series of steps into a compound called pyruvate. Glycolysis consumes two ATP molecules but produces four, thus providing a net gain of two ATPs. If oxygen is present, the process is called aerobic glycolysis and the pyruvate product then enters a reaction called the tricarboxylic (TCA) cycle, also known as the citric acid cycle or the Krebs cycle. The TCA cycle uses oxygen extracted from hemoglobin in the blood to oxidize pyruvate, and a network of proteins in the cell mitochondria, known as the electron transport chain, passes electrons across a series of compounds to release energy, which in turn is used by an enzyme known as ATP synthase to generate an additional 34 ATP molecules. So, while glycolysis itself produces only 2 ATP molecules from each glucose molecule, the addition of oxygen allows the production of a total of 36 ATP molecules from each molecule of glucose.

If oxygen is not present, the pyruvate is reduced to an end product, lactate, in a process called anaerobic glycolysis. During strenuous exercise when the sup-
ply of oxygen from the lungs is insufficient, anaerobic glycolysis occurs in muscles, and it is the buildup of lactate that can cause pain and fatigue. Lactate is removed from the muscles by the vascular system. While anaerobic glycolysis is a relatively inefficient source of ATP, it is quite fast; it can occur at a rate about 100 times faster than the oxidation of pyruvate into ATP through the TCA cycle and the electron transport chain. In addition, some cells can convert lactate back into pyruvate and use it in the TCA cycle to produce more ATP.

The energy provided by ATP supports many aspects of brain physiology: housekeeping functions related to the synthesis of proteins, the maintenance and turnover of membranes, axoplasmic transport, and the synthesis, packaging, and breakdown of neurotransmitters. Yet, the lion’s share of energy goes to restoring unequal distributions of ions following EPSPs, IPSPs, and action potentials. The gray matter of the brain consumes about 30 to 50 μmol of ATP every minute for each gram of tissue (i.e., 30 to 50 μmol/g/min of ATP), while a brain in coma consumes only about 10 μmol/g/min of ATP. Thus, integrative and signaling activities in neurons should account for about 75% of the energy expenditure in gray matter, while housekeeping functions account for only about 25%.

Moreover, because the chemical reactions associated with neuronal integration and signaling are well known, researchers can determine how much of the brain’s energy budget supports different processes. In a 2001 study based on data from the rodent brain, Attwell and Laughlin estimated that the restoration of membrane concentration gradients following the passage of an action potential consumes 47% of the energy expenditure, while restoring postsynaptic membrane concentration gradients following IPSPs and EPSPs consumes 34% (Figure 6.6). The authors commented that the energy cost of IPSPs is probably less than that of EPSPs for two reasons: Cl⁻ ions move down a smaller electrochemical gradient than the Na⁺ ions, and inhibitory synapses are out-
Figure 6.6 The energy budget of the (rodent) brain. Data from the rodent brain, shown here, indicates that the vast majority of energy is required to support the restoration of concentration gradients following action potentials and postsynaptic potentials. While human data are not available for these categories, the differences in brain structure between humans and rodents suggests that the proportion of energy needed for restoring gradients after postsynaptic potentials is even greater in humans. These results indicate that the primary energy expenditure of the brain supports the integrative and signaling roles of neurons. (Data from Atwell and Laughlin, 2001.)

numbered by excitatory synapses in the brain by about one order of magnitude. The maintenance of the resting potential in neurons and glia was estimated to consume 13% of the energy expenditure. Note that the consumption of energy in each of these processes principally involves the operation of the sodium–potassium pump. Furthermore, given that glutamate is by far the dominant excitatory neurotransmitter in the brain, most of the energy budget associated with signaling and integration involves this single neurotransmitter. The uptake, breakdown, and repackaging of glutamate was estimated to consume 3% of the energy budget, and restoring Ca^{2+} fluxes in presynaptic membranes accounted for the remaining 3%.

In extrapolating their results to primates, these authors argued that the greater number of synapses per neuron in primates would cause a greater proportion of the energy budget to be spent on restoring postsynaptic concentration gradients, perhaps as much as 74%. They concluded, therefore, that the metabolic demands of the integrative and signaling activities of neurons form the bulk of the energy requirements of the human brain. To meet these energy demands, the vascular system must ensure a continuous supply of glucose and oxygen.

The Vascular System of the Brain

The idea that changes within the vascular system of the brain reflect changes in brain function is not new. The nineteenth-century British physiologists Roy and Sherrington postulated that changes in activity associated with specific brain functions might result in locally increased blood flow:

These facts seem to us to indicate the existence of an automatic mechanism by which the blood supply of any part of the cerebral tissue is varied in accordance with the activity of the chemical changes which underlie the functional action of that part. Bearing in mind that strong evidence exists of localisation of function in the brain, we are of the opinion that an automatic mechanism, of the kind just referred to, is well fitted to provide for a local variation of the blood supply in accordance with local variations of the functional activity. (1890, p.105)
A variant of this idea, that activity could cause changes in blood flow, was tested in an experiment conducted by the Italian physiologist Angelo Mosso around that same time. Mosso had pioneered the measurement of comparative blood volume in the brain and extremities, and he was interested in whether thinking resulted in increased blood flow to the brain. His earlier studies had revealed that blood flow to the brain decreases during sleep and increases with waking, consistent with the idea that brain activity requires a greater blood supply than inactivity. To directly test the hypothesis that active thought requires increased blood volume in the brain, Mosso constructed an ingenious apparatus (Figure 6.7), as reported by William James in his Principles of Psychology:

The subject to be observed lay on a delicately balanced table which could tip downward either at the head or at the foot if the weight of either end were increased. The moment emotional or intellectual activity began in the subject, down went the balance at the head end, in consequence of the redistribution of blood in his system. (1890, p. 98)

Such a result, if observed, would have provided strong evidence for a relationship between vascular changes and cognitive function. Yet, the reported results were almost certainly overstated. For the table to tip downward, the brain's total blood volume, not local blood flow, would need to increase by an appreciable amount. But overall blood volume is relatively constant over time, even if local blood flow changes in response to metabolic demands. To use a hydraulic analogy, if pipes are filled with water, they will weigh essentially the same regardless of whether the water is flowing quickly or slowly. Nevertheless, the idea that changes in blood flow may result from local functional changes in the brain was a remarkable insight. The discussion of this issue in James's Principles, especially the difference between causal and correlational roles for blood flow, is highly recommended to the interested student. We explore the relationship between blood flow and brain function in the following sections, leading to the idea that the functional activity of neurons may evoke changes in blood flow and thus changes in the local concentrations of metabolites.
Figure 6.8 Blood supply to the human cerebrum. As illustrated here, the surface pattern of blood supply to the human cerebrum is highly complex. The red vessels are tributaries of the middle cerebral artery, the yellow vessels are tributaries of the anterior cerebral artery, and the blue vessels are tributaries of the posterior cerebral artery. The veins are shown in black. (After Duvernoy, Delon, and Vannson, 1981.)

Arteries, capillaries, and veins

From our discussion earlier in this chapter, we know that the integrative and signaling activities of neurons constitute a large proportion of the brain's energy budget, and we also know that there is little energy stored in the brain. The energy needs of neurons and glia are met by the ATP created during glycolysis and during the subsequent oxidation of pyruvate. The oxygen and glucose fuel required for those reactions is delivered through the vascular system (Figure 6.8). In the adult human brain, about 54 mL of blood flows through each 100 g of tissue every minute. This adds up to about 800 mL/min for the average 1400 g brain, and represents about 15 to 20% of the blood flow in the entire human body. Thus, although the brain constitutes a mere 2 to 3% of total body weight, it consumes about 20% of blood oxygen.

The lungs are the source of the oxygen carried by the blood. Oxygen diffuses from the alveoli of the lungs, via small blood vessels, into red blood cells, where it binds to hemoglobin. Four oxygen molecules are attached to each hemoglobin molecule, and there are about 280 million hemoglobin molecules in each red blood cell. The oxygen-rich blood returns to the heart from the lungs, where it enters the left atrium, moves to the left ventricle, and is pumped from the left ventricle through the aorta. The aorta gives rise to several large arteries: thick-walled vessels that carry blood away from the heart. Each artery branches into smaller arteries and then to even smaller arterioles that eventually terminate in capillaries. The change in scale as these vessels branch is remarkable. The diameter of the aorta in an adult human is about 2.5 cm (about one inch); typical large arteries can be 4 to 10 mm in diameter; while the diameters of arterioles are in the range of 10 to 50 μm. Thus, the largest artery has a diameter about 2500 times that of the smallest arteriole!

The extraction of oxygen and glucose from the blood and the removal of waste carbon dioxide occurs at the surfaces of the capillaries. Capillaries are thin-walled vessels comparable in diameter (5 to 10 μm) to the width of a red blood cell (about 7.5 μm), which actually deform as they move through the narrowest capillaries. The small sizes of individual capillaries is more than made up for by their number and density (Figure 6.9). It has been estimated that any cell in the body is, on average, less than 50 μm from a capillary. If lined up end to end, the capillary network in the human body would stretch 60,000 miles and have a total surface area of 800 to 1000 m². Capillary density in a particular part of the body roughly indicates its cellular metabolism in that
area. Areas with high metabolism have higher capillary densities than those with lower metabolic rates. For example, in the cat brain, gray matter, composed of neural cell bodies, has twice the capillary density of white matter, which is composed largely of axonal processes.

**Thought Question**

Many techniques in fMRI attempt to localize hemodynamic activity to the capillaries. Why is this desirable for studies of brain function?

Following oxygen extraction, the deoxygenated hemoglobin molecules, which now bind waste carbon dioxide, are carried from the capillaries to small venules that are comparable in size to arterioles. The venules collect into larger and larger veins that eventually return the oxygen-poor blood through the vena cava to the heart. The deoxygenated blood then travels to the lungs, where the waste carbon dioxide is released and where oxygen binds to the hemoglobin to start the cycle again.

**Arterial and venous anatomy of the human brain**

The flow of blood to the brain is supplied by two major arterial systems: the left and right internal carotid arteries and the vertebral/basilar arteries (Figure 6.10). A short distance from the heart, the aortic arch gives rise to the right

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**Figure 6.9** Capillary structure. This electron microscope image shows the density of capillary beds within the cortex. (From Duvernoy, Delon, and Vannson, 1981.)

**Figure 6.10** The arterial system of the human brain. The arterial distribution of blood to the human brain is shown in cross-section (A), and in a ventral view of the base of the brain (B). The box highlights the anastomoses of the basilar artery and internal carotid arteries that form the circle of Willis.
circle of Willis. The interconnection between the basilar artery and the carotid arteries at the base of the cranial vault.

sinuses. The term sinus has two primary meanings in neuroanatomy: (1) long venous channels formed by meningeal coverings that form the primary draining system for the brain, and (2) air-filled cavities in the skull.

and left common carotid arteries, which ascend in the neck before each divides into the external and internal carotid arteries. The external carotid arteries supply the external head and face with blood, while the internal carotid arteries enter the skull through an opening in the base called the foramen lacerum and supply blood to the brain. The aortic arch also gives rise to the right and left subclavian arteries, which, in turn, give rise to the left and right vertebral arteries, which run along the anterior surface of the spinal cord and enter the brain through the foramen magnum. The vertebral arteries give rise to the descending arterial branches, which provide blood to the brain stem, medulla, and spinal cord. As the vertebral arteries ascend to the level of the pons, they fuse into the single basilar artery, which gives rise to arterial branches that perfuse the pons and cerebellum.

The basilar artery interconnects, or forms an anastomosis, with the left and right internal carotid arteries to form the circle of Willis, named for the celebrated English physician Thomas Willis, who first illustrated this vascular structure in 1664. The circle of Willis sits on the floor of the cranial vault, surrounding the brainstem. Supplied by blood from both arterial systems, it gives rise bilaterally to the anterior, middle, and posterior cerebral arteries (Figure 6.11A and B). Each of these major cerebral arteries supplies blood to a distinct region of the brain. The anterior cerebral artery primarily supplies the medial surface of the brain and the head of the caudate, branches of the middle cerebral artery supply much of the lateral and superior cerebral cortex as well as the remainder of the basal ganglia, and the posterior cerebral artery supplies the posterior temporal and occipital cortex. This specificity has important implications for neurology, in that strokes within particular arteries tend to affect particular regions of the cortex and thus have functionally distinct cognitive consequences.

The venous drainage of the brain’s circulation (Figure 6.11C and D) is accomplished through the left and right jugular veins, which exit the skull base through the jugular foramen, then join with the subclavian vein and eventually the superior vena cava, progressing to the right atrium and ventricle of the heart, which pumps blood to the lungs for reoxygenation. The jugular veins themselves are fed by the sinus system of the brain. Sinuses are long venous channels that are formed by the meningeal covering of the brain. The superior sagittal sinus runs along the superior midline of the entire brain, where the two hemispheres meet. Large cerebral veins on the cortical surface drain into the superior sagittal sinus, and blood is transported back along the sinus to the back of the brain. The inferior sagittal sinus follows a similar midline path that followed by the superior sagittal sinus, but deeper in the brain in the part of the dura mater called the falx, which extends down into the midline separating the cerebral hemispheres. The inferior sagittal sinus empties into the straight sinus, which runs back above the cerebellum and joins with the superior sagittal sinus at the back of the brain to form the transverse sinus. The transverse sinus wraps around to the left and right of the base of the brain, terminating in the left and right internal jugular veins.

Microcirculation

The blood supply to the cerebral and cerebellar cortices is derived from meningeal arteries that traverse the cortical surface (Figure 6.12). A distinction can be drawn between conducting and distributing arteries. Conducting arteries run for long distances along the pial surface and are about 700 μm in diameter (i.e., narrower than the 4 to 5 mm diameters of the internal carotid and basilar arteries). In the cerebral cortex, many conducting arteries run along the
Figure 6.11 The arterial (red) and venous (blue) organization of the cerebral vasculature. Shown are lateral (A) and medial (B) views of the major arterial systems of the human brain. Blood is drained by a system of sinuses and veins, shown here in lateral (C) and medial (D) views.

...sulci that demarcate adjacent gyri, while others run directly across the gyral surface. Many shorter and smaller distributing arteries, each about 150 to 200 μm in diameter, branch from the conducting arteries. Many researchers have noted constrictions where the distributing arteries branch from larger arteries, suggesting the presence of muscular sphincters that could control blood flow. The distributing arteries continue to ramify on (or branch over) the cortical surface into yet smaller precortical arteriole of about 50 to 70 μm in diameter. Anastomoses, or branches and reconnections, between arterioles have been observed in several studies. According to Nonaka and colleagues, a distributing artery supplies a 3.5-by-2-mm area on the cortical surface, while each precortical artery supplies an approximately 1-by-1-mm area of cortical surface. Each precortical artery then ramifies into smaller arterioles of about 30 to 40 μm diameter that penetrate the cortical surface at right angles.
Figure 6.12 Microcirculation in the human brain. The distributions of arteries (red) and veins (black) on the medial orbital gyrus of the human brain are illustrated in (A). A photograph of the same region is provided in (B). (From Duvernoy, Delon, and Vannson, 1986.)

As part of their seminal studies of the brain’s vascular system, Duvernoy and colleagues documented the properties of these intracortical arterioles. Most small arterioles vascularize the gray matter, with increasing vessel diameters in those that vascularize deeper layers. The density of vascularization is not uniform across cortical layers; noticeably denser vascularization is observed where the highest concentrations of neural cell bodies are located (Figure 6.13). Some intracortical vessels have been described as resembling a fountain or candelabra, with dense ramifications ascending into more superficial layers. Still other intracortical arterioles, those with the largest diameters, appear to penetrate straight through the cortex to vascularize the white matter below. Vascularization in the white matter is considerably less dense than in the gray matter.

Blood Flow

Neuronal activity evokes changes in blood flow (i.e., the volume of moving blood per unit time) by changing both the volumes of blood vessels and the velocity with which blood moves through those vessels. These quantities vary considerably within the vascular system due to many physical and physiological factors: blood pressure; the
diameter of the blood vessel; the density of the red blood cells; the amount of oxygen and carbon dioxide in the blood; and the age, health, and activity level of the subject. Peak flow velocity in the aorta can exceed 90 cm/s. Using a technique called transcranial Doppler, researchers have measured the mean blood flow velocity in the basilar and internal carotid arteries at about 40 cm/s. Blood flow through the smaller arteries and arterioles is considerably slower, ranging from 10 to 250 mm/s, and blood flow through the capillaries can be less than 1 mm/s. As the blood collects in venules and travels to larger veins, the velocity once again increases to a range of 10 to 250 mm/s, which is still considerably slower than within the arterial system. These values are approximate, because the estimated velocity of blood flow depends on how it is measured.

Holding other factors constant, blood flow is proportional to the pressure difference from one end of the vessel to the other, divided by the resistance of the vessel to flow. As a result, flow is proportional to vessel radius expressed to the fourth power, so very small changes in vessel diameter can produce large changes in resistance and flow. For example, doubling the size of the vessel would increase flow by a factor of 16. In large arteries, blood flow is pulsatile due to the pumping of the heart, and flow velocity can vary greatly between the peak flow measures obtained during systole and the lower velocities measured during diastole.

The small arteries on the pial surface have high resistance and thus oppose flow. These resistance vessels help convert the pulsatile ejection of blood from the heart into a steady flow through the capillaries. Indeed, if no resistance were present and high blood pressure persisted into the capillaries, blood plasma would be pushed through the thin capillary walls, leading to a considerable loss of blood volume and concomitant damage. Thus, small resistance vessels are an important component in the control of blood flow through the capillary bed.

**Control of blood flow**

Functionally specific changes in blood flow are believed to be initiated when active neurons release substances that diffuse through the extracellular space and reach nearby blood vessels. These vasoactive substances cause the vessels to dilate, and because the increase in diameter reduces the vessels' resistance, flow increases. However, this local change is not sufficient by itself to regulate blood flow, because flow is also influenced by the higher-resistance arterioles located on the pial surface, which can be well upstream and distant from the active neurons. Thus, there needs to be coordination between the local blood flow changes induced by neural activity and upstream control mechanisms.

Several candidate mechanisms have been identified for the local control of blood flow (see Box 6.1). These include potassium ions (K⁺), which enter the extracellular space as a result of synaptic activity, and adenosine, which is created during the dephosphorylation of ATP, and which increases in concentration during times of high metabolic activity. Other research has focused on nitric oxide, which is released by the activation of both local and distant neurons. Nitric oxide mediates both local and distal vasodilation (or increase in the size of blood vessels) by causing the smooth muscle cells surrounding arterioles to relax. Gap junctions between endothelial cells in arteries propagate the vasodilatory response upstream, causing increased blood flow to larger arteries. This propagated action initiated by nitric oxide along the arterioles shares conceptual similarities with the propagation of neuronal action potentials. Even more exciting, resistance vessels Arterioles that control the flow of blood through the capillary bed.

**vasoactive substances** Substances that change the diameter of blood vessels.
Many cortical vessels are surrounded by intertwining processes arising from neurons and glial cells, raising the possibility that some aspects of blood flow may be controlled by neurons themselves, either directly or indirectly. For example, some large pial arteries receive projections from cranial nerves and sensory ganglia, and these projections surround the smooth muscles that encase the vessel. Studies have shown that the neurotransmitters released by these projections can dilate or constrict the vessel. However, the relationship between neurogenic control of blood flow and local brain function remains unclear. Given that these large vessels supply extensive regions of cortex, changes in their flow must be shaped by local resistance vessels to direct the blood flow to the active neuronal region.

Substantial research has implicated specific neurotransmitters in the local control of blood flow. As one example, Krimer and colleagues examined the role of dopamine, which is produced centrally by small clusters of midbrain neurons that project broadly to the striatum and cerebral cortex. Using histological staining techniques, light microscopy, and electron microscopy, these investigators demonstrated that dopamine terminals are found in apposition to small intracortical arterioles and capillaries. Moreover, at capillaries, the dopamine terminals are apposed to pericytes, contractile elements that can constrict or dilate the capillary and thus influence local flow patterns (Figure 1). The direct application of dopamine onto small cortical arterioles caused a constriction of the diameter of the vessels that started about 18 to 40 s after application onset and reached a maximum constriction of 18 to 24%. Full recovery occurred after several minutes. The time course of these changes is slower than the change in the BOLD-contrast fMRI signal, which can peak 4 to 5 s after the onset of a stimulus. However, these data raise the interesting possibility that neurons could influence blood flow independently of local neuronal activity, perhaps in anticipation of upcoming needs. Such centrally stimulated blood flow changes might be associated with long-duration changes in MRI signal that are maintained over many minutes. If true, this would require a refinement of our idea that the BOLD signal is strictly related to the energy needs of active neurons. Addition-

![Figure 1 Evidence of direct innervation of capillaries by dopaminergic neurons. (A) An electron micrograph that shows a large dopamine terminal (arrow) adjacent to a capillary. As can be seen in the light-microscopic inset, which shows a cross section of the same spatial location, the terminal lies along this capillary over a large spatial extent. (B) An enlargement of this dopamine terminal. The terminal is separated from the basal lamina (b) of the blood vessel by only a process from an adjacent pericyte (p), a cell with contractile properties. The inset in (C) shows a light-microscopic image depicting a string of three terminals adjacent to a capillary. The electron micrograph in (C), enlarged in (D), shows that one of the terminals is directly apposed to the basal lamina of the capillary. (From Krimer et al., 1998.)](image)
Figure 2  Astrocytes mediate changes in vessel diameter, in response to local neuronal activity. (A) Researchers measured the width of an arteriole in a live mouse brain (top) with high temporal resolution, using a technique known as two-photon microscopy. The cross-section of that arteriole increased following electrical stimulation (indicated by lightning bolt), which led to the release of calcium ions within the surrounding astrocytes (specifically, within processes known as endfeet that surround the arteriole). The maximum diameter was reached about 3–6 s later. Shown at right are enlargements of the arteriole at three points in time. (B) Moreover, direct neuronal stimulation caused an increase in the diameter of the arterioles (dashed line indicates original size of vessel). (After Takano et al., 2006.)

Studies have provided evidence that blood flow is influenced by other neurotransmitters, including serotonin, acetylcholine, and norepinephrine. Also possible are less direct effects: neuronal activity may trigger changes in nearby glial cells, which in turn cause dilation in nearby blood vessels. In a compelling 2006 study, Takano and colleagues used a high-resolution technique known as two-photon imaging to identify the role of one type of glial cell, the astrocyte, in the local control of blood flow in anesthetized mice. The authors labeled astrocytes with a chemical that was sensitive to changes in local calcium, and then selectively released calcium (Ca\(^{2+}\)) to visualize rapid changes in the astrocytes and in the blood vessels they were in contact with. They found that release of Ca\(^{2+}\)-triggered vasodilation. Local arterioles increased in cross-sectional area by about 18%, while blood flow increased by 37%. The timing of these changes were consistent with known hemodynamic properties (Figure 2A), in that increases in calcium concentration preceded changes in vessel diameter by only about 500 ms, and full dilation followed within a few seconds. Then, they stimulated the brain directly using an electrode, and found increases in astrocytic calcium concentrations, dilation of blood vessels, and increased blood flow (Figure 2B). Through

(continued on next page)
a series of tests, they showed that specific chemicals could selectively suppress the increase in blood flow through their effects on the astrocytes, without altering the neuronal activity. They concluded that local changes in blood flow are mediated, at least in part, by chemical signals from active neurons (likely via the synaptic release of glutamate) that lead to increases in Ca\(^{2+}\) in astrocytes, which in turn increase the diameters of nearby vessels.

This study, among several others, points to an important new direction for understanding how neuronal activity leads to changes in blood flow. There now exists substantial evidence that local changes in blood flow reflect neurovascular coupling, likely through intervening glial cells that can influence the diameter of nearby arterioles. While the work of Takano and colleagues focused on rapid dilation associated with increased activity, other studies have illustrated other aspects of what seems to be a complex system for dilating and constricting blood vessels based on metabolic demands. As noted in a 2004 in vitro study by Mulligan and MacVicar, the effects of calcium may be mediated by the neurotransmitter norepinephrine, through broad neuronal projections from a midbrain structure known as the locus coeruleus that targets the astrocytes. This brain structure supports, among other capacities, changes in the overall arousal and alertness of an organism. Thus, the changes in blood flow measured in fMRI likely reflect the complex interactions among neuronal activity, neurotransmitter release, nearby glial cells, the response properties of the local vasculature, and even systemic changes that may predict future metabolic demands. Given these effects, researchers are exploring ways of calibrating fMRI data by accounting for baseline blood flow when estimating task-related changes in cerebral energy metabolism, as advanced by Hyder and colleagues. Clearly, given the rapid pace of discovery in this area, these experimental manipulations along with future studies will clarify this picture and may suggest unexpected new contributors to the control of blood flow.

Some recent studies have demonstrated that changes in calcium concentration, triggered by neuronal activation, may lead to dilation of nearby blood vessels.

Animal studies by many investigators have demonstrated the effects of neuronal activity on local blood flow. Ngai and colleagues applied low-intensity somatosensory stimulation to the sciatic nerve of the rat while monitoring the pial vasculature through a window cut into the skull. The time courses of vascular diameter and blood flow were measured in response to 20 s periods of stimulation. Vascular diameter increased rapidly with the onset of stimulation, reaching a peak 5.5 s later. The diameter of the artery increased from a mean of 33 \(\mu\)m at baseline to a peak of about 44 \(\mu\)m, an increase of about 33%. After reaching its early peak, the diameter contracted to a plateau about 10% above baseline until the stimulation ended. The blood flow measures showed a very similar time course (Figure 6.14). Thus, in response to a sensory stimulus, the pial arteries dilate and blood flow increases. The authors also investigated the issue of the spatial extent, or coarseness, of these flow-related changes. Localizing the active neurons by measuring evoked field potentials, the authors noted that the vasodilatory response was remarkably discrete in its anatomic distribution, and that other arterioles branching from the same distribution artery, but that perfused other parts of somatosensory cortex, did not dilate (Figure 6.15).

Similar findings were obtained by Iadecola and colleagues. Electrical stimulation of parallel fibers in the rat’s cerebellum produced focal neuronal stimulation that was exquisitely localized using evoked field potential mapping. The authors found that the arterioles supplying the activated neurons dilated
Figure 6.14 The relationship between sensory stimulation and local blood flow changes. The sciatic nerve of the rat was stimulated (solid horizontal line below graph in part A) and the time course of arteriole dilation (A) and blood velocity (B) were measured in the somatosensory cortex. The neuronal stimulation increased both diameter and flow. No change in mean arterial blood pressure (C) accompanied these functional vascular changes. (Data from Ngai, Morii, and Winn, 1988.)

by up to 26%. Larger arterioles upstream from the activated site showed smaller diameter increases of about 8%. No field potentials were recorded in the vicinity of these larger arterioles, which were about 2 to 3 mm distant (Figure 6.16). This result demonstrated that blood flow can increase in vessels that are upstream of the local neuronal activity. In subsequent studies, these upstream responses were found to be highly attenuated in mice that were genetically deficient in an enzyme responsible for the production of nitric oxide. Thus, these data support the role of nitric oxide in triggering blood flow increases through the control of upstream resistance vessels.

These data also put limits on the spatial specificity of hemodynamic changes as an indicator of neuronal activity. While the epicenter of the blood flow response was in the region of synaptic activity, arteriolar dilation and increased blood flow were also observed a few millimeters distant, where there was no synaptic activity. Iadecola and colleagues noted that neuronal activity produces a hemodynamic change over an area that is larger than the area of increased neuronal activity. This emphasizes that the distribution of hemodynamic responses measured using functional neuroimaging techniques will be ultimately determined by the local architecture of the microvascular blood supply.

Thought Question

Why do the results of Iadecola and colleagues limit the spatial resolution of neuroimaging techniques that depend on hemodynamic changes?

Effects of increased blood flow on capillaries

As we have reviewed, increased neuronal activity leads to increased blood flow in the arterioles that supply those neurons, and such increases in flow can occur in vessels up to several millimeters distant from the epicenter of neuronal activity. The effects of this increased blood flow on capillaries, venules,
Figure 6.15 The change in diameter of arterioles following sciatic (hindlimb) stimulation. Arterioles that perfuse the cortical region corresponding to the hindlimb of the rat ($A_1$ and $A_2$), increase in diameter. Nearby vessels (B) and those that perfuse the forepaw region (C and D) do not increase in diameter. (After Ngai, Morii, and Winn, 1988.)

Figure 6.16 Change in arteriole dilation as a function of distance from active neurons. Changes in diameter of blood vessels on the surface of the rat's cerebellum during parallel fiber stimulation were measured. Neuronal field potential activity was recorded at the black dot. Shown in this schematic diagram is an arteriole (center) passing over larger draining veins. Numbers indicate the mean diameter (± standard error) of the arteriole, and percentages indicate the change in that diameter with stimulation, at different points along its branches. As might be expected, the largest dilations occurred in the immediate vicinity of the neuronal stimulation. However, upstream vessels 2 to 3 mm from the site of activity (i.e., to the right on this figure) also showed modest dilation, even though there was no evoked activity nearby. (After Ladecola et al., 1997.)
and veins is less well understood. In the studies discussed in the previous section, the diameters of both arterioles and venules were measured in response to stimulation, and while arterioles dilated, no such effect was observed for venules. Many other studies have measured relative dilation of both arterioles and venules in response to physiological manipulations, such as hypocapnia (low levels of CO₂ in the blood), hypercapnia (excessive CO₂ in the blood), and pharmacological manipulations in which drugs were locally injected in the vessel. In general, these studies have shown that while venules do dilate, they do to a much lesser extent than arterioles. For example, under hypercapnia, the diameters of arterioles that were normally 10 to 30 μm in diameter increased by 50%, while similarly sized venules increased in diameter by only 10%.

What are the consequences in the capillary bed for this increased blood flow from the arterioles? One popular hypothesis is that a large reserve of unperfused (i.e., unfilled) capillaries is available to accept this increased flow, leading to an increase in total blood volume within the capillaries. This hypothetical phenomenon, known as capillary recruitment, may seem plausible. Yet in vivo studies with capillary staining and high-resolution microscopic techniques provide contradictory evidence: nearly all capillaries in the brain are perfused, the proportion of perfused capillaries does not change according to arousal state (e.g., sleeping vs. wakefulness), and increased blood flow has minimal effects on capillary perfusion. Thus, capillary recruitment can be rejected as a model for hemodynamic changes following neuronal activity. Another possibility is that individual capillaries distend slightly and thus decrease their resistance to flow, leading to increased flow within those capillaries and, again, increased overall blood volume within the capillary bed. Studies that have manipulated the amount of CO₂ dissolved in the blood to stimulate vessel contraction and dilation have reported that capillaries can, in fact, alter their diameters by about 20% between the physiologically extreme conditions of hypocapnia and hypercapnia. This capillary distension would increase the surface areas of individual capillaries, which could increase the area available for the transfer of oxygen and glucose to active neurons. The degree to which this occurs during normal physiological conditions, however, is not known.

The most likely result of increased flow into the capillaries is the regularization of flow velocity. Individual capillaries exhibit remarkable heterogeneity in their flow velocities. Some capillaries have very high rates of flow, while others have very low rates. With increased flow, the distribution of flow velocities increases and becomes more uniform. This process bears conceptual similarities to capillary recruitment, as discussed in the previous paragraph. However, unlike models of capillary recruitment, this scenario presumes that all vessels are perfused at some baseline level. Thus, the principal response of the capillary bed to increased blood flow appears to be an increase in overall flow velocity, with an unknown contribution from capillary distension. One consequence of this increased rate of flow is that the transit time of hemoglobin molecules through the capillaries decreases, which might affect the likelihood that an individual hemoglobin molecule would exchange its oxygen with an active neuron. We resume this story in Chapter 7, where we discuss how the properties of oxygenated and deoxygenated hemoglobin can be measured by MRI, to allow mapping of brain function onto brain structure (see Box 6.2 for an overview).
BOX 6.2 Primer on Neuroanatomy

Throughout this book, we will be making frequent reference to neuroanatomical terms, and frequent use of neuroanatomical terms. After all, our subject is functional brain imaging! While a detailed treatment of human neuroanatomy is beyond the scope of this book, here we present a brief overview sufficient for the discussions in this text.

Taken together, the brain and spinal cord form the central nervous system, or CNS. Special, sometimes confusing terms are often used to describe the relative locations of anatomical structures. Imagine that the CNS is a long cylinder that rises as a vertical column from the beginning of your spinal cord near your tailbone into your skull, and then bends 90° toward your nose. Along this axis, the term caudal, from the Latin term for "tail," refers to the direction of the tail or hind limbs. The term rostral, derived from the Latin term for "beak," refers to the direction of the nose. Again relative to this axis, dorsal refers to the back while ventral refers to the front. So your chest is ventral to your back, and your back is dorsal to your chest (cf., the dorsal fin of sharks). Once inside the brain, where the axis of the CNS bends 90°, dorsal structures are now superior and ventral structures are inferior. So the top of your brain is dorsal to the bottom of your brain, and the bottom of your brain is ventral to the top of your brain. Structures that are closer to the midline of the brain are medial, and structures that are closer to the edge of the brain are lateral.

The CNS is composed of a number of cellular elements. The principal information-processing cells of the CNS are called neurons, which have cell bodies and protoplasmic processes called dendrites and axons (see the main text for a more complete description). Areas within the CNS composed primarily of cell bodies are sometimes called gray matter, while areas composed primarily of large axon bundles are called white matter. The white matter is so named due to the color of myelin, the fatty sheath that encases the axons of many neurons and speeds the propagation of action potentials. The myelin sheath is constructed by a support cell called the oligodendrocyte. Another type of support cell found in the CNS is the astrocyte, which helps regulate the extracellular environment within the CNS, including changes in blood flow (see Box 6.1). The supporting oligodendrocytes and astrocytes are known collectively as glial cells, or glia (from the Greek for "glue").

Neurons come in different sizes, shapes, and typical patterns of connectivity. Two common neuron types are pyramidal cells, named for the triangular shape of their cell bodies, and stellate cells, which have more spherical cell bodies. Pyramidal cells have long axons that can travel great distances within the brain, while stellate cells appear to play a primary role in local processing.

Three membranes, or meninges, cover the outside surface of the brain and spinal cord. The outermost covering is called the dura, which is quite thick and tough. The middle layer is called the arachnoid, its weblike appearance being the source of its name. The innermost layer is called the pia, which is a delicate membrane that closely adheres to the contours of the brain. The pia is highly vascularized and, as discussed in the main text, is the source of the small arteries that supply the cortex. The space between the arachnoid and pia is filled with cerebrospinal fluid, or CSF, a colorless liquid that bathes the brain and spinal cord. CSF is produced in the choroid plexus, an invagination of the pia into the ventricles of the brain. The ventricles are a continuous series of cavities within the brain that are filled with CSF. The CSF flows down from the two lateral ventricles, through the midline third ventricle, into the fourth ventricle in the central nervous system (CNS). The brain and spinal cord.

caudal Toward the back of the brain.
rostral Toward the front of the brain.
dorsal Toward the top of the brain.
ventral Toward the bottom of the brain.
medial Toward the middle of the brain.
lateral Toward the side of the brain.
myelin A fatty substance that forms sheaths surrounding axons that serve to speed the transmission of action potentials.
oligodendrocyte A type of glial cell that constructs the myelin sheaths around axons.
astrocyte A type of glial cell that regulates the extracellular environment.
dura The outermost membrane covering the brain; its name comes from its thickness and toughness.
arachnoid The middle membrane covering the brain; its name comes from its weblike appearance.
pia The innermost membrane covering the brain; it closely adheres to the brain’s contours.
cerebrospinal fluid (CSF) A colorless liquid that surrounds the brain and spinal cord and fills the ventricles within the brain.

ventricles Fluid-filled cavities within the brain.
region of the brain stem (see the next section), and then into the cisterns, where it flows both upward to bathe the surfaces of the cerebrum and downward into the spinal cord. The CSF is eventually absorbed into the vascular system in the superior sagittal sinus, part of the venous drainage system of the brain found between layers of the dura. The CSF forms a fluid cushion that protects the brain, particularly from its bony encasement. It also serves to maintain a consistent external environment for the cells of the CNS and helps remove metabolic wastes.

**Major Components of the CNS**

Figure 1 shows an MRI of the head taken along the midline and thus bisecting the brain. A view of the brain in any parallel plane is called a sagittal view and this specific slice is known as a mid-sagittal view. The position of the brain within the head and skull can be well appreciated in this view, which also provides a convenient starting place for describing the major subdivisions of the CNS.

The most caudal aspect of the CNS visible in Figure 1 is the spinal cord, which can be seen entering the brain through an opening within the base of the skull called the foramen magnum (unlabeled, but located just above the line indicating the position of the spinal cord). The spinal cord contains ascending sensory fiber tracts that transmit somatosensory information to the brain from sensors throughout the body, and descending motor fiber tracts that transmit control information to the muscles from the brain. Just rostral to the foramen magnum is a continuation of the spinal cord called the medulla oblongata. The medulla contains the cell bodies for several major cranial nerves, some of which are involved in the control of respiration, circulation, and vegetative functions. In many texts, the medulla is also referred to as the myelencephalon (in Greek, *enkephalos* means "in the head or brain"), one of the five major subdivisions of the brain.

The pons is a prominent structure just rostral to the medulla. Like the medulla, the pons is a thoroughfare that is traversed by many ascending sensory and descending motor fiber tracts. The pons also contains the cell bodies that are the source of cranial nerves that innervate the face and eye muscles.

Just posterior and intimately connected through thick fiber bundles to the pons is the cerebellum, which is a large structure important in the coordination of walking and posture, motor learning, and even complex cognitive functions. The cerebellum is located within a part of the skull called the posterior fossa, which is separated from the remainder of the brain by a tough membrane called the tentorium. Together, the pons and cerebellum comprise the metencephalon. Collectively, the metencephalon and myelencephalon are sometimes called the hindbrain.

Rostral to the pons is the midbrain, or mesencephalon (see Figure 6). The midbrain gives rise to two major cranial nerves and also contains several impor-
BOX 6.2 (continued)

tant cell clusters or nuclei, including the red nucleus and substantia nigra. The latter is a major source of dopamine in the brain; loss of cells in the substantia nigra can cause Parkinson’s disease, a serious affliction of aging that is associated with tremor and a progressive deterioration of motor control. The superior and inferior colliculi are paired structures located on the posterior aspect of the midbrain (they appear as small bumps on the back of the midbrain in Figure 1). The superior colliculi are part of the visual system, while the inferior colliculi are part of the auditory system.

The midbrain, pons, and medulla contain clusters of neurons that comprise the ascending reticular formation, which is important in regulating sleep, arousal, and levels of consciousness. Many neuroanatomists refer collectively to the midbrain, pons, and medulla as the brain stem, as it appears to support the more rostral brain as a stem supports a flower.

Rostral to the midbrain are the hypothalamus and thalamus, which together with the epithalamus and pineal gland constitute the diencephalon. The hypothalamus is involved in autonomic functions and somatic functions, including the regulation of temperature, water intake, and hunger. The hypothalamus is also an important structure in the regulation of endocrine functions—particularly in its control of the pituitary gland.

The thalamus is a paired structure connected at the midline by the massa intermedia. The thalamus is composed of a large number of nuclei that are sometimes referred to as relay nuclei because they receive information from sensory, motor, and other regions of the brain, organize or process this information, and then project the information to specific regions of cortex. For example, the lateral geniculate is a nucleus of the thalamus that receives and processes visual information from the eyes before projecting that information to the visual cortex. Similar functions are carried out by the medial geniculate for auditory information and by the ventral posterolateral nucleus for the somatosensory system. Some thalamic nuclei are involved in relaying motor information in the brain. For example, the ventral lateral nuclei receive motor information from the cerebellum and project it to the motor cortex. Other thalamic nuclei appear to integrate information from other brain regions that are neither motor nor sensory. For example, the dorsomedial nucleus receives information from the amygdala, hypothalamus, and other thalamic nuclei and projects this information to the frontal lobes.

Rostral to the diencephalon is the telencephalon, or forebrain. The telencephalon is the largest, most complex, and most evolutionarily advanced part of the brain. It is composed of the cerebral cortical hemispheres (the cerebrum), older layered structures like the hippocampus, and large subcortical nuclei such as the amygdala and the basal ganglia (itself composed of the caudate, putamen, and globus pallidus). Interconnecting these brain regions are extensive white-matter tracts, which can be seen in Figure 2.

brain stem The midbrain, pons, and medulla.

hypothalamus A brain nucleus that supports homeostatic functions, including the regulation of food and water intake.

thalamus A brain nucleus that is important for many aspects of perception and cognition; it is highly interconnected with many regions of the cerebral cortex.

basal ganglia A set of nuclei in the forebrain that includes the caudate, putamen, and globus pallidus.

Figure 2 A sagittal drawing of the white-matter tracts of the human cerebral cortex. (From Ludwig and Klioner, 1956.)
BOX 6.2 (continued)

The Cortex

The cerebral hemispheres (cerebrum) are composed of a continuous sheet of cerebral cortex that has been folded into an undulating pattern of gyri and sulci. Gyri are rises of cortex that are separated by infolded troughs, or sulci. If unfolded and laid out as a sheet, the cortex of the average human brain would have an area of 2500 cm². The most evolutionarily recent region of the cortex is called the neocortex, which is about 5 mm thick and composed of six layers, or lamina (Figure 3). Layer I is the closest to the pial surface and is composed primarily of axonal and dendritic processes with few neurons. Layers II and III are composed primarily of pyramidal cells, and the cells in Layer II have smaller cell bodies than those of Layer III. Layer IV is relatively devoid of pyramidal cells but is densely packed with stellate cells. Layer IV contains projections from other cortical regions and thus appears to be the primary input layer of the cortex. Layer IV appears to project primarily to Layers I, II, and III, which appear to comprise the intracortical processing layers. Layers V and VI contain large pyramidal cells that project their axons to other brain regions and thus appear to represent the output layers of the neocortex. Note that although few fMRI studies distinguish between these layers given that the typical voxel size is on the order of several millimeters, other techniques like electrophysiologic single cell recording are able to do so. (See Chapter 8 for a few intriguing examples in which fMRI is used to distinguish between cortical layers.)

Cortical thickness, packing density, and composition and size of constituent cells differ across the various regions of the cortex. Anatomists have developed detailed maps of the cortex based on these differences in cytoarchitecture, with the hope of differentiating function on the basis of structure. One popular cytoarchitectonic map published by Korbinian Brodmann in 1909 divides the cerebral cortex into 47 different regions (Figure 4). These regions, or Brodmann areas, are used today in many studies to communicate the locations of brain activation measured by fMRI or by positron emission tomography (PET).

Although no non-invasive neuroscience method can measure the cytoarchitecture of the brain directly, sufficient similarities exist between individuals to permit the use of spatial transformations.

cerebrum The two hemispheres forming the major part of the brain.
gyri Rises in the cortical surface.
sulci Troughs in the cortical surface.
cytoarchitecture The organization of the brain on the basis of cell structure.
Brodmann areas Divisions of the brain based on the influential cytoarchitectonic criteria of Korbinian Brodmann.

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that warp an individual's brain into a common atlas space (such as the atlas of Talairach and Tournoux) that has been annotated with Brodmann areas.

Although the cortical sheet is continuous, the presence of several deep fissures in the typical brain has resulted in the subdivision of the brain into four major lobes: the frontal, parietal, temporal, and occipital lobes—so named for the skull bones that cover them. A fifth lobe, the insula, is hidden behind part of the anterior temporal lobe and inferior frontal lobe. Some neuroanatomists also describe a limbic lobe that is composed of midline structures including the cingulate cortex, hippocampus, and amygdala. The cerebral hemispheres and their constituent lobes and nuclei are paired structures. Although the two hemispheres appear roughly similar in shape, there are subtle anatomical differences between them that most likely form the basis for such lateralized functions as language and spatial skills.

The left lateral surface of the cerebral hemisphere with meninges and blood vessels removed is shown in Figure 5. The locations of the frontal, parietal, occipital, and temporal lobes are shown.

The precentral and postcentral gyri are separated by the central sulcus, a deep fissure that separates the frontal and parietal lobes. The gyrus anterior to the central sulcus—the precentral gyrus—is often described as the primary motor cortex. Along its medial to lateral extent is a somatotopic representation of the body, or homunculus, with the lower extremities represented near the midline, the hands in the middle, and the mouth and tongue near its most lateral extent. Electrical stimulation of this gyrus causes involuntary movement of the represented limb. The gyrus posterior to the central sulcus—the postcentral gyrus—has a sensory representation of central sulcus. A deep fissure that separates the frontal and parietal lobes of the brain.

Figure 4 The cytoarchitectonic map of Brodmann (1909).

Figure 5 Surface view of the left hemisphere of the human brain. (Courtesy of S. Mark Williams and Dale Purves, Duke University Medical Center.)
the body that is closely aligned to the motor representation just described. Electrical stimulation of the postcentral gyrus causes a tingling sensation in a particular body part.

The temporal lobe is separated from the frontal and parietal lobes by the deep Sylvian fissure. The lateral part of the temporal lobe plays an important role in auditory and visual processing, and the temporal lobe in the left hemisphere is particularly important for language processing. The occipital lobe at the posterior end of the brain is the primary region of the brain for visual processing. It is separated from the parietal lobe by the parieto-occipital fissure, which is best seen in the medial view presented in Figure 6. The parietal lobe plays an important role in spatial processing, among many other functions. The frontal lobes are quite large and have many functions. The dorsal lateral frontal lobe plays an important role in complex cognitive processing including executive functions like reasoning and decision making. Within the left frontal lobe in most individuals is a region supporting language production known as Broca’s area. The more ventral and medial parts of the frontal lobe appear to play a role in emotional processing. The insula, not visible in Figure 5 (see Figure 8), is hidden deep within the anterior part of the Sylvian fissure and inferior frontal lobe. The insula is important for the chemical senses such as olfaction and gustation, but also plays an important role in a wide range of affective processes from evaluating fear and pain to avoiding risky situations.

The corpus callosum is a large white-matter bundle that connects the hemispheres of the brain (it can be easily seen in Figure 6). The most anterior part of the corpus callosum is known as the genu, while the posterior enlargement is called the splenium.

Figure 7 presents two views of the ventral surface of the brain. The photographed brain in Figure 7A has the cerebellum attached, but the surface blood vessels have been removed. The drawing in Figure 7B has omitted the cerebellum so that the gyri and sulci on the ventral surface of the temporal lobe can be identified. Many regions in the inferior temporal lobe play an important role in higher visual processes, including the perception of complex objects. The entorhinal cortex and parahippocampal gyrus, along with the adjacent hippocampus (not shown), are.

**Figure 6** Midsagittal view of the human brain. (Courtesy of S. Mark Williams and Dale Purves, Duke University Medical Center.)

(continued on next page)
collectively referred to as the medial temporal lobe and support memory processes.

Figure 8 and Figure 9 present two brain slices that have orthogonal orientations frequently used in MRI. Figure 8 is an axial view taken at one slice within the dorsal–ventral plane, in which rostral is at the top of the image and caudal is at the bottom of the image. Figure 9 is a coronal view taken at one slice within the rostral–caudal plane, in which the dorsal is up and the ventral is down. In both the coronal and axial views, the midline of the brain is the midline of the view. Visible is a clear distinction between the thin layer of cortical gray matter and the deep white-matter tracts; it is clear that the cortex in the deep sulci is continuous with the cortex of the gyri. The insula is visible as an island of cortex hidden behind the outer surfaces of the temporal and frontal lobes. Also visible are the basal ganglia (caudate and putamen), which are important for motor control and play key roles in many cognitive processes associated with learning.

The lateral ventricles are clearly visible in Figure 9 near the center of the brain. Also visible is the anterior end of the brain. A horizontal view of the brain (along the x–y plane in MRI).

coronal A frontal view of the brain (along the x–z plane in MRI).

Figure 7 Ventral view of the human brain. Shown in (A) is a photograph of the ventral surface, with the cerebellum and brain stem visible. The drawing in (B) has the cerebellum removed, so that gyri can be identified. (A courtesy of S. Mark Williams and Dale Purves, Duke University Medical Center.)
the amygdala, which supports emotion-
al processing and is an important com-
ponent of the limbic lobe. Notable in
this coronal view are the interhemi-
spheric white matter tracts. The corpus
callosum forms by far the largest such
connection, with the anterior commis-
sure a secondary but still important
source of communication between the
hemispheres.

Figure 8 Axial view of the human brain
at the level of the anterior commissure.
(Courtesy of S. Mark Williams and Dale
Purves, Duke University Medical Center.)

Figure 9 Coronal view of the human
brain at the level of the anterior com-
missure. (Courtesy of S. Mark Williams and
Dale Purves, Duke University Medical
Center.)
Summary

The fundamental element of information processing in the human brain is the neuron. Neurons have two primary roles, integration and signaling, which rely on changes in cell membrane potential and the release of neurotransmitters. While the integrative and signaling activities themselves do not require external sources of energy, the restoration of ionic concentration gradients following these activities does require an energy supply. The primary metabolites supplied to active neurons are glucose and oxygen, which together are important for the synthesis of ATP. These metabolites are supplied via the vascular system. The main components of the vascular system are arteries, capillaries, and veins, each present at different spatial scales. Changes within the vascular system in response to neuronal activity may occur in brain areas far from the neuronal activity, initiated in part by flow-controlling substances released by neurons into the extracellular space, or by direct influences from neurons or nearby glial cells. Neurons may directly alter flow in pial arteries, arterioles, and capillaries, but it is unknown whether such effects have consequences for fMRI measurements. A major consequence of the vascular response to neuronal activity is the arterial supply of oxygenated hemoglobin, from which oxygen is extracted in the capillaries. These changes in the local concentration of deoxygenated hemoglobin provide the basis for fMRI.

Suggested Readings


*James, W. (1890). The Principles of Psychology. Dover, New York. The masterwork of a scientist who integrated brilliant introspections with a keen experimental sense, this classic compendium still provides useful insights on a wide range of topics. The chapter on brain physiology is highly recommended.


*Indicates a reference that is a suggested reading in the field and is also cited in this chapter.
Chapter References


