blood-oxygenation-level dependent (BOLD) contrast. The difference in signal on $T_2^*$-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.

deoxygenated hemoglobin can be used to construct images based upon blood-oxygenation-level dependent (BOLD) contrast. It is important to recognize that BOLD contrast is a consequence of a series of indirect effects. It results from changes in the magnetic properties of water molecules, which in turn reflect the influence of paramagnetic deoxyhemoglobin, which is a physiological correlate of oxygen consumption, which itself is a correlate of a change 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 ensembles of neurons comprising a functional network? Understanding the answers to these questions is critical for being both an informed user of fMRI methods and an informed consumer of fMRI results. We consider, in this chapter and the next, the links between neuronal activity, energy consumption, cerebral metabolism, blood flow, and MR signal.

Neuronal Activity

We begin this inquiry with the neuron (Figure 6.2), the basic information-processing unit of the central nervous system, focusing on the relation 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 19 billion to 23 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 with 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 have protoplasmic processes called axons that transmit information to other neurons at specialized locations on their dendrites and cell bodies.
Neurons come in many varieties, some with dense dendritic arbor 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.

To a useful first approximation, neuronal activity can be characterized as either integrative or signaling. Integrative activity collects inputs from other neurons through connections on both dendrites and the cell body. Signaling activity results primarily from activity of axons, which transmit the outcome of integrative processes to one or more other neurons. The transfer of information between neurons occurs at specialized junctions called synapses, where the ending of an axonal process from one neuron (i.e., the presynaptic terminal) is apposed 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.

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 a concentration gradient from areas of high concentration to areas of low concentration.

ion A charged atom.

don 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 gradient.

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

tact and electrical 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 upon 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, though, 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 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 species of ions can pass and others cannot. Furthermore, channels have gating mechanisms that can close them 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 gradient, membranes also contain transporters, or pumps, that can move ions across the membrane against their concentration gradient 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, as well as to 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 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.

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.
While the diffusion of substances through channels down their concentration gradients requires only sufficient kinetic energy from heat, 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 (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 locus 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 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 neuron. This influx of Na\(^+\) ions decreases the electrical potential between the inside and outside of the membrane at the channel location. (Note that another type of glutamate receptor called the NMDA [N-methyl-D-aspartate] receptor admits Ca\(^{2+}\) 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, or 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 limited event. Afterward, the neurotransmitter will be deactivated or removed from the synaptic cleft and receptor, the channel that was opened by the neurotransmitter will close, and the 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 throughout its dendritic trees and soma. 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.
Figure 6.4 Synapses and neurotransmitter release.

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. This wave of depolarization, known as a nerve impulse or
action potential, sweeps down the axon in a self-propagating manner, indepen-
dently 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-depend-
ent 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 neurotransmitter into the synaptic cleft, which interacts
with receptors that gate postsynaptic ion channels, and thus initiates either
an IPSP or EPSP on the postsynaptic membrane of the target neuron.

One can think of information processing by neurons as the combination
of their integrative and signaling roles. The spatiotemporal pattern of EPSPs
and IPSPs, each generated at a synapse from another cell, determines the rela-
tive polarization of the neuron. If the axon hillock region of the neuron
becomes sufficiently depolarized, an action potential occurs and the polar-
izations of other neurons are influenced by the action of that action potential
upon their postsynaptic membranes. 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 region 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.

The generation of an EPSP, IPSP, or action potential does not in itself
require an external source of energy, because the associated movements of
ions are along concentration gradients. However, these 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 mem-
brane potential of the neuron, so electrical gradients now oppose the reentry
of the positively charged K\(^+\) into the cell. To restore the asymmetric distribu-
tion of Na\(^+\) and K\(^+\) across the cell membrane and restore the resting mem-
brane 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
requirements for restoration of these concentration gradients are discussed
in the next section.

Cerebral Metabolism: Neuronal Energy Consumption

Although integrative and signaling properties of neurons are ultimately
important for understanding brain function, our immediate interest is in
their energy requirements. Why are the energy demands of neurons important
for fMRI? To help answer this question, imagine that neurons have suffi-
cient local stores of energy available to buffer moderate changes in their
neuronal firing rates. Could we then construct meaningful theories of brain
function based upon energy delivery by the blood supply? Or imagine that
it were known that the main consumption of energy following neuronal firing
was to increase the synthesis of protein, perhaps related to 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 the generation of action potentials accounted for
a tiny fraction, less than 3%, of the brain’s energy budget. How then would
one account for the enormous metabolic demands of the active brain?