have seen dramatic progress, leading to the identification of dozens of definitive risk genes and chromosomal regions.

3. The maturation of the field of psychiatric genetics and genomics over the past decade has revealed the frailty of testing pre-specified candidate genes. These types of studies have now been supplanted by genome-wide scans of both common and rare alleles. Coupled with rigorous statistical frameworks and consensus statistical thresholds, these are yielding highly reliable and reproducible results.
4. At present, the cumulative evidence suggests that the full range of genetic variations underlies complex behavioral syndromes, including common and rare, transmitted and de novo, germline and somatic, and sequence and chromosomal structural variation. However, the relative contributions of these various types of genetic changes vary for a given disorder.
5. A striking finding from recent advances in the genetics of human behavior has been the overlap of genetic risks for syndromes with distinct symptoms and natural histories. Understanding how and why an identical mutation may lead to highly diverse phenotypic outcomes in different individuals will be a major challenge for the future.
6. Findings across common psychiatric disorders point to extremely high rates of genetic heterogeneity. This, coupled with the biological pleiotropy of the risk genes that have been identified to date, as well as the dynamism and complexity of human brain development, all point to important challenges ahead in moving from an understanding of risk genes to an understanding of behavior. Similarly, at present, an important distinction can be made between illuminating the biology of risk genes and unraveling the pathophysiology of behavioral syndromes.

Glossary[1]

Allele. Humans carry two sets of chromosomes, one from each parent. Equivalent genes in the two sets might be different, for example, because of single nucleotide polymorphisms. An allele is one of the two (or more) forms of a particular gene.

Centromere. Chromosomes contain a compact region known as a centromere, where sister chromatids (the two exact copies of each chromosome that are formed after replication) are joined.

Cloning. The process of generating sufficient copies of a particular piece of DNA to allow it to be sequenced or studied in some other way.

Complementary DNA (cDNA). A DNA sequence made from a messenger RNA molecule, using an enzyme called *reverse transcriptase*. cDNAs can be used experimentally to determine the sequence of messenger RNAs after their introns (non–protein-coding sections) have been spliced out.

Conservation of genes. Genes that are present in two distinct species are said to be conserved, and the two genes from the different species are called *orthologous genes*. Conservation can be detected by measuring the similarity of the two sequences at the base (RNA or DNA) or amino acid (protein) level. The more similarities there are, the more highly conserved the two sequences.

Copy number variation (CNV). A deletion or duplication of a limited genetic region that results in an individual having more or fewer than the usual two copies of some genes. Copy number variations are observed in some neurological and psychiatric disorders.

CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats). An enzyme-RNA system in which the enzyme cleaves target sequences that match an RNA guide; the RNA guide can be engineered to recognize a desired gene or sequences within a cell for mutation.

Euchromatin. The gene-rich regions of a genome (see also heterochromatin).

Eukaryote. An organism with cells that have a complex internal structure, including a nucleus. Animals, plants, and fungi are all eukaryotes.

Genome. The complete DNA sequence of an organism.

Genotype. The set of genes that an individual carries; usually refers to the particular pair of alleles (alternative forms of a gene) that a person has at a given region of the genome.

Haplotype. A particular combination of alleles (alternative forms of genes) or sequence variations that are closely linked—that is, are likely to be inherited together—on the same chromosome.

Heterochromatin. Compact, gene-poor regions of a genome, which are enriched in simple sequence repeats.

Introns and exons. Genes are transcribed as continuous sequences, but only some segments of the resulting messenger RNA molecules contain information that encodes a protein product. These segments are called *exons*. The regions between exons are known as *introns* and are spliced from the RNA before the product is made.

[1]Based on Bork P, Copley R. 2001. Genome speak. Nature 409:815.

Long and short arms. The regions on either side of the centromere are known as arms. As the centromere is not in the center of the chromosome, one arm is longer than the other.
Messenger RNA (mRNA). Proteins are not synthesized directly from genomic DNA. Instead, an RNA template (a precursor mRNA) is constructed from the sequence of the gene. This RNA is then processed in various ways, including splicing. Spliced RNAs destined to become templates for protein synthesis are known as mRNAs.
Mutation. An alteration in a genome compared to some reference state. Mutations do not always have harmful effects.
Phenotype. The observable properties and physical characteristics of an organism.
Polymorphism. A region of the genome that varies between individual members of a population. To be called a polymorphism, a variant should be present in a significant number of people in the population.
Prokaryote. A single-celled organism with a simple internal structure and no nucleus. Bacteria and archaebacteria are prokaryotes.
Proteome. The complete set of proteins encoded by the genome.
Recombination. The process by which DNA is exchanged between pairs of equivalent chromosomes during egg and sperm formation. Recombination has the effect of making the chromosomes of the offspring distinct from those of the parents.
Restriction endonuclease. An enzyme that cleaves DNA at a particular short sequence. Different types of restriction endonuclease cleave at different sequences.
RNA interference (RNAi). A method for reducing the function of a specific gene by introducing into a cell small RNAs with complementarity to the targeted mRNA. Pairing of the mRNA with the small RNA leads to destruction of the endogenous mRNA.
Single nucleotide polymorphism (SNP). A polymorphism caused by the change of a single nucleotide. SNPs are often used in genetic mapping studies.
Splicing. The process that removes introns (noncoding portions) from transcribed RNAs. Exons (protein-coding portions) can also be removed. Depending on which exons are removed, different proteins can be made from the same initial RNA or gene. Different proteins created in this way are *splice variants* or *alternatively spliced*.
Transcription. The process of copying a gene into RNA. This is the first step in turning a gene into a protein, although not all transcripts lead to proteins.
Transcriptome. The complete set of RNAs transcribed from a genome.
Translation. The process of using a messenger RNA sequence to synthesize a protein. The messenger RNA serves as a template on which transfer RNA molecules, carrying amino acids, are lined up. The amino acids are then linked together to form a protein chain.

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3

Nerve Cells, Neural Circuitry, and Behavior

The remarkable range of human behavior depends on a sophisticated array of sensory receptors connected to the brain, a highly flexible neural organ that selects from among the stream of sensory signals those events in the environment and in the internal milieu of the body that are important for the individual. The brain actively organizes sensory information for perception, action, decision-making, aesthetic appreciation, and future reference—that is to say, memory. It also ignores and discards information judiciously, one hopes, and reports to other brains about some of these operations and their psychological manifestations. All this is accomplished by interconnected nerve cells.

Individual nerve cells, or neurons, are the basic signaling units of the brain. The human brain contains a huge number of these cells, on the order of 86 billion neurons, that can be classified into at least a thousand different types. Yet this great variety of neurons is less of a factor in the complexity of human behavior than is their organization into anatomical circuits with precise functions. Indeed, one key organizational principle of the brain is that nerve cells with *similar* properties can produce different actions because of the way they are interconnected.

Because relatively few principles of organization of the nervous system give rise to considerable functional complexity, it is possible to learn a great deal about how the nervous system produces behavior by focusing on five basic features of the nervous system:

1. The structural components of individual nerve cells;
2. The mechanisms by which neurons produce signals within themselves and between each other;
3. The patterns of connection between nerve cells and between nerve cells and their targets (muscle and gland effectors);
4. The relationship of different patterns of interconnection to different types of behavior; and
5. How neurons and their connections are modified by experience.

The parts of this book are organized around these five major topics. In this chapter, we introduce these topics in turn in an overview of the neural control of behavior. We first consider the structure and function of neurons and the glial cells that surround and support them. We then examine how individual cells organize and transmit signals and how signaling between a few interconnected nerve cells produces a simple behavior, the knee-jerk reflex. We then extend these ideas to more complex behaviors, mediated by more complex and malleable circuits.

The Nervous System Has Two Classes of Cells

There are two main classes of cells in the nervous system: nerve cells, or neurons, and glial cells, or glia.

Nerve Cells Are the Signaling Units of the Nervous System

A typical neuron has four morphologically defined regions: (1) the cell body, (2) dendrites, (3) an axon, and (4) presynaptic terminals (Figure 3–1). As we shall see, each region has a distinct role in generating signals and communicating with other nerve cells.

The cell body or *soma* is the metabolic center of the cell. It includes the nucleus, which contains the genes of the cell, and the endoplasmic reticulum, an extension of the nucleus where the cell's proteins are synthesized. The cell body usually gives rise to two kinds of processes: several short *dendrites* and one long, tubular *axon*. Dendrites branch out in tree-like fashion and are the main apparatus for receiving incoming signals

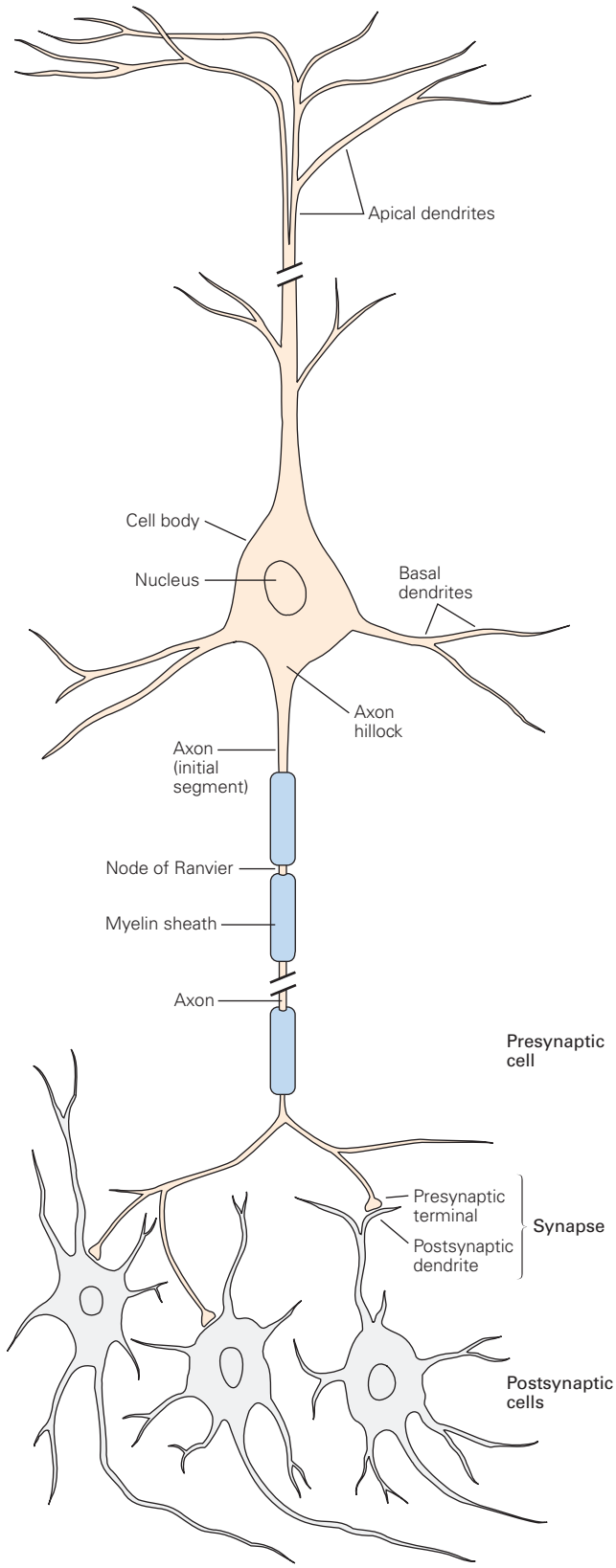

Figure 3–1 (Right) The structure of a neuron. Most neurons in the vertebrate nervous system have several main features in common. The cell body contains the nucleus, the storehouse of genetic information, and gives rise to two types of cell processes: axons and dendrites. Axons are the transmitting element of neurons; they vary greatly in length, some extending more than 1 m within the body. Most axons in the central nervous system are very thin (between 0.2 µm and 20 µm in diameter) compared with the diameter of the cell body (50 µm or more). Many axons are insulated by a sheath of fatty myelin that is regularly interrupted at gaps called the nodes of Ranvier. The action potential, the cell's conducting signal, is initiated at the initial segment of the axon and propagates to the synapse, the site at which signals flow from one neuron to another. Branches of the axon of the presynaptic neuron transmit signals to the postsynaptic cell. The branches of a single axon may form synapses with as many as 1,000 postsynaptic neurons. The apical and basal dendrites together with the cell body are the input elements of the neuron, receiving signals from other neurons.

from other nerve cells. The axon typically extends some distance from the cell body before it branches, allowing it to carry signals to many target neurons. An axon can convey electrical signals over distances ranging from 0.1 mm to 1 m. These electrical signals, or *action potentials*, are initiated at a specialized trigger region near the origin of the axon called the *initial segment* from which the action potentials propagate down the axon without failure or distortion at speeds of 1 to 100 m/s. The amplitude of an action potential traveling down the axon remains constant at 100 mV because the action potential is an all-or-none impulse that is regenerated at regular intervals along the axon (Figure 3–2).

Action potentials are the signals by which the brain receives, analyzes, and conveys information. These signals are highly stereotyped throughout the nervous system, even though they are initiated by a great variety of events in the environment that impinge on our bodies—from light to mechanical contact, from odorants to pressure waves. The physiological signals that convey information about vision are identical to those that carry information about odors. Here we see a key principle of brain function: the type of information conveyed by an action potential is determined not by the form of the signal but by the pathway the signal travels in the brain. The brain thus analyzes and interprets patterns of incoming electrical signals carried over specific pathways, and in turn creates our sensations of sight, touch, taste, smell, and sound.

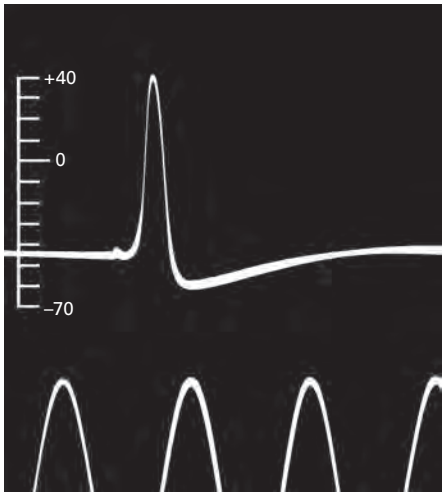

Figure 3–2 This historic tracing is the first published intracellular recording of an action potential. It was recorded in 1939 by Alan Hodgkin and Andrew Huxley from a squid giant axon, using glass capillary electrodes filled with sea water. The timing pulses (bottom) are separated by 2 ms. The vertical scale indicates the potential of the internal electrode in millivolts, the sea water outside being taken as zero potential. (Reproduced, with permission, from Hodgkin and Huxley 1939.)

To increase the speed by which action potentials are conducted, large axons are wrapped in an insulating sheath of a lipid substance, myelin. The sheath is interrupted at regular intervals by the nodes of Ranvier, uninsulated spots on the axon where the action potential is regenerated. (Myelination is discussed in detail in Chapters 7 and 8 and action potentials in Chapter 10.)

Near its end, the axon divides into fine branches that contact other neurons at specialized zones of communication known as *synapses*. The nerve cell transmitting a signal is called the *presynaptic cell*; the cell receiving the signal is the *postsynaptic cell*. The presynaptic cell transmits signals from specialized enlarged regions of its axon's branches, called *presynaptic terminals* or *nerve terminals*. The presynaptic and postsynaptic cells are separated by a very narrow space, the *synaptic cleft*. Most presynaptic terminals end on the postsynaptic neuron's dendrites, but some also terminate on the cell body or, less often, at the beginning or end of the axon of the postsynaptic cell (see Figure 3–1). Some presynaptic neurons excite their postsynaptic target cells; other presynaptic neurons inhibit their target cells.

The neuron doctrine (Chapter 1) holds that each neuron is a discrete cell with distinctive processes arising from its cell body and that neurons are the signaling units of the nervous system. In retrospect, it is hard to appreciate how difficult it was for scientists to accept this elementary idea when first proposed. Unlike other tissues, whose cells have simple shapes and fit into a single field of the light microscope, nerve cells have complex shapes. The elaborate patterns of dendrites and the seemingly endless course of some axons made it extremely difficult to establish a relationship between these elements. Even after the anatomists Jacob Schleiden and Theodor Schwann put forward the cell theory in the early 1830s—and the idea that cells are the structural units of all living matter became a central dogma of biology—most anatomists did not accept that the cell theory applied to the brain, which they thought of as a continuous, web-like reticulum of very thin processes.

The coherent structure of the neuron did not become clear until late in the 19th century, when Ramón y Cajal began to use the silver-staining method introduced by Golgi. Still used today, this method has two advantages. First, in a random manner that is not understood, the silver solution stains only about 1% of the cells in any particular brain region, making it possible to examine a single neuron in isolation from

its neighbors. Second, the neurons that do take up the stain are delineated in their entirety, including the cell body, axon, and full dendritic tree. The stain reveals that there is no cytoplasmic continuity between neurons, and Cajal concluded, prophetically and correctly, that there is no continuity even at synapses between two cells.

Ramón y Cajal applied Golgi's method to the embryonic nervous systems of many animals as well as humans. By examining the structure of neurons in almost every region of the nervous system, he could describe classes of nerve cells and map the precise connections between many of them. In this way, Ramón y Cajal deduced, in addition to the neuron doctrine, two other principles of neural organization that would prove particularly valuable in studying communication in the nervous system.

The first of these, the *principle of dynamic polarization*, states that electrical signals within a nerve cell flow in only one direction: from the postsynaptic sites of the neuron, usually the dendrites and cell body, to the trigger region at the axon. From there, the action potential is propagated along the entire length of the axon to its terminals. In most neurons studied to date, electrical signals in fact travel along the axon in one direction.

The second principle advanced by Ramón y Cajal, *connectional specificity*, states that nerve cells do not connect randomly with one another in the formation of networks but make specific connections—at particular contact points—with certain postsynaptic target cells and not with others. The principles of dynamic polarization and connectional specificity are the basis of the modern cellular-connectionist approach to studying the brain.

Ramón y Cajal was also among the first to realize that the feature that most distinguishes one type of neuron from another is form, specifically the number of the processes arising from the cell body. Neurons are thus classified into three large groups: unipolar, bipolar, and multipolar.

Unipolar neurons are the simplest because they have a single primary process, which usually gives rise to many branches. One branch serves as the axon; other branches function as receiving structures (Figure 3–3A). These cells predominate in the nervous systems of invertebrates; in vertebrates, they occur in the autonomic nervous system.

Bipolar neurons have an oval soma that gives rise to two distinct processes: a dendritic structure that receives signals from other neurons and an axon that carries information toward the central nervous system (Figure 3–3B). Many sensory cells are bipolar, including those in the retina and olfactory epithelium of the nose. The receptor neurons that convey touch, pressure, and pain signals to the spinal cord develop initially as bipolar cells, but the two cell processes fuse into a single continuous structure that emerges from a single point in the cell body, and the dendrite is endowed with the specializations that render it an axon. In these so-called pseudo-unipolar cells, one axon transmits information from the sensory receptors in the skin, joints, and muscle toward the cell body, while the other carries this sensory information to the spinal cord (Figure 3–3C).

Multipolar neurons predominate in the nervous system of vertebrates. They typically have a single axon and many dendritic structures emerging from various points around the cell body (Figure 3–3D). Multipolar cells vary greatly in shape, especially in the length of their axons and in the extent, dimensions, and intricacy of their dendritic branching. Usually the extent of branching correlates with the number of synaptic contacts that other neurons make onto them. A spinal motor neuron with a relatively modest number of dendrites receives about 10,000 contacts—1,000 on the cell body and 9,000 on dendrites. In Purkinje cells in the cerebellum, the dendritic tree is much larger and bushier, receiving as many as a million contacts!

Nerve cells are also classified into three major functional categories: sensory neurons, motor neurons, and interneurons. *Sensory neurons* carry information from the body's peripheral sensors into the nervous system for the purpose of both perception and motor coordination. Some primary sensory neurons are called *afferent neurons*, and the two terms are used interchangeably. The term *afferent* (carried toward the central nervous system) applies to all information reaching the central nervous system from the periphery, whether or not this information leads to sensation. The term *sensory* designates those afferent neurons that convey information to the central nervous system from the sensory epithelia, from joint sensory receptors, or from muscle, but the concept has been expanded to include neurons in primary and secondary cortical areas that respond to changes in a sensory feature, such as displacement of an object in space, a shift in sound frequency, or the angular rotation of the head (via vestibular organs in the ear) or even something as complex as a face.

The term *efferent* applies to all information carried from the central nervous system toward the motor organs, whether or not this information leads to action. *Motor neurons* carry commands from the brain or spinal cord to muscles and glands (efferent information). The traditional definition of a *motor neuron* (or motoneuron) is a neuron that excites a muscle, but the designation of motor neuron now includes other

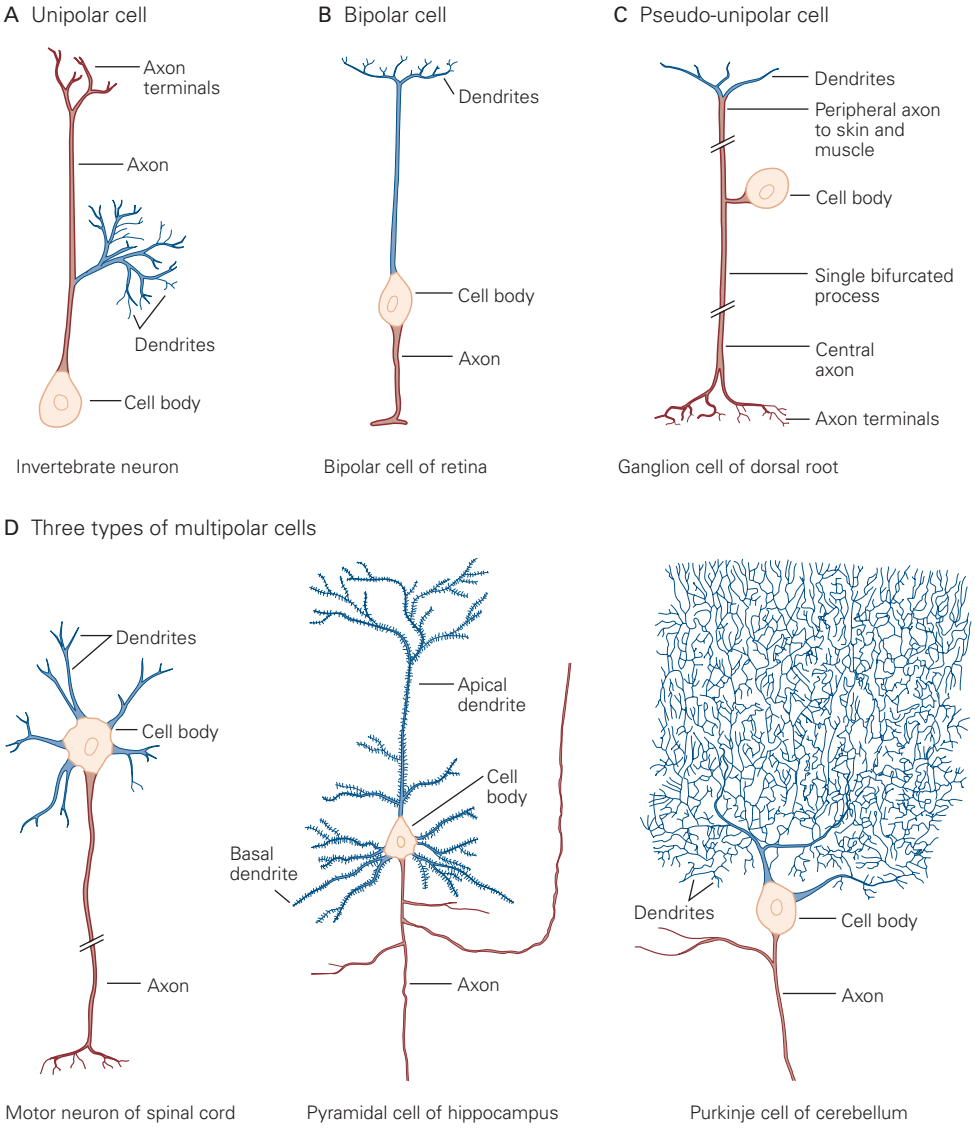

Figure 3–3 Neurons are classified as unipolar, bipolar, or multipolar according to the number of processes that originate from the cell body.

A. Unipolar cells have a single process emanating from the cell. Different segments serve as receptive surfaces or releasing terminals. Unipolar cells are characteristic of the invertebrate nervous system.

B. Bipolar cells have two types of processes that are functionally specialized. The dendrite receives electrical signals and the axon transmits signals to other cells.

C. Pseudo-unipolar cells, which are variants of bipolar cells, carry somatosensory information to the spinal cord. During development, the two processes of the embryonic bipolar cell fuse and emerge from the cell body as a single process that has two functionally distinct segments. Both segments function as axons; one extends to peripheral skin or muscle, the other to the central spinal cord. (Adapted, with permission, from Ramón y Cajal 1933.)

D. Multipolar cells have a single axon and many dendrites. They are the most common type of neuron in the mammalian nervous system. Three examples illustrate the large diversity of these cells. Spinal motor neurons innervate skeletal muscle fibers. Pyramidal cells have a roughly triangular cell body; dendrites emerge from both the apex (the apical dendrite) and the base (the basal dendrites). Pyramidal cells are found in the hippocampus and throughout the cerebral cortex. Purkinje cells of the cerebellum are characterized by a rich and extensive dendritic tree that accommodates an enormous number of synaptic inputs. (Adapted, with permission, from Ramón y Cajal 1933.)