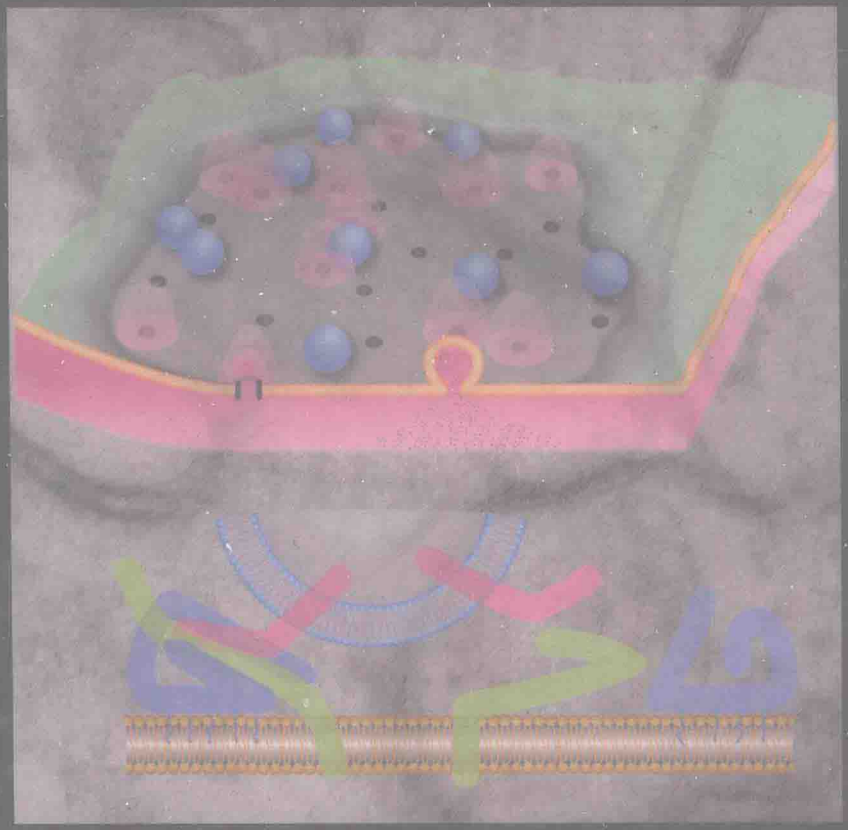
从分子到网络

细胞和分子神经科学导论

From Molecules to Networks

An Introduction to Cellular and Molecular Neuroscience



Edited by John H. Byrne and James L. Roberts

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FROM MOLECULES TO NETWORKS
An Introduction to Cellular and Molecular Neuroscience

从分子到网络
细胞和分子神经科学导论

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This textbook is dedicated to our wives, Susan and Poco

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Preface

The past twenty years have witnessed an exponential increase in the understanding of the nervous system at all levels of analyses. Perhaps the most striking developments have been in the understanding of the cell and molecular biology of the neuron. The field has moved from treating the neuron as a simple black box that added up impinging synaptic input to fire an action potential to one in which the function of nerve cells involves a host of biochemical and biophysical processes that act synergistically to process, transmit and store information. In this book, we have attempted to provide a comprehensive summary of current knowledge of the morphological, biochemical, and biophysical properties of nerve cells. The book is intended for graduate students, advanced undergraduate students, and professionals. The chapters are highly referenced so that readers can pursue topics of interest in greater detail. We have also included material on mathematical modeling approaches to analyze the complex synergistic processes underlying the operation and regulation of nerve cells. These modeling approaches are becoming increasingly important to facilitate the understanding of membrane excitability, synaptic transmission, as well gene and protein networks. The final chapter in the book illustrates the ways in which the great strides in understanding the biochemical and biophysical properties of nerve cells have led to fundamental insights into an important aspect of cognition, memory.

We are extremely grateful to the many authors who have contributed to the book, and the support and encouragement during the two past years of Jasna Markovac and Johannes Menzel of Academic Press. We would also like to thank Evangelos Antzoulatos, Evyatar Av-Ron, Diasinou Fioravanti, Yoshihisa Kubota, Rong-Yu Liu, Fred Lorenzetii, Riccardo Mozzachiodi, Gregg Phares, Travis Rodkey, and Fredy Reyes for help with editing the chapters.

John H Byrne

James L Roberts

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Cellular Components of Nervous Tissue

Patrick R. Hof, Bruce D. Trapp, Jean de Vellis, Luz Claudio, and David R. Colman

Several types of cellular elements are integrated to yield normally functioning brain tissue. The neuron is the communicating cell, and a wide variety of neuronal subtypes are connected to one another via complex circuitries usually involving multiple synaptic connections. Neuronal physiology is supported and maintained by the neuroglial cells, which have highly diverse and incompletely understood functions. These include myelination, secretion of trophic factors, maintenance of the extracellular milieu, and scavenging of molecular and cellular debris from it. Neuroglial cells also participate in the formation and maintenance of the blood–brain barrier, a multicomponent structure that is interposed between the circulatory system and the brain substance and that serves as the molecular gateway to the brain parenchyma.

THE NEURON

Neurons are highly polarized cells, meaning that they develop, in the course of maturation, distinct subcellular domains that subserve different functions. Morphologically, in a typical neuron, three major regions can be defined: (1) the cell body, or perikaryon, which contains the nucleus and the major cytoplasmic organelles; (2) a variable number of dendrites, which emanate from the perikaryon and ramify over a certain volume of gray matter and which differ in size and shape, depending on the neuronal type; and (3) a single axon, which extends in most cases much farther from the cell body than does the dendritic arbor (Fig. 1.1). The dendrites may be spiny (as in pyramidal cells) or nonspiny (as in most interneurons), whereas the axon is generally smooth and emits a variable number of branches (collaterals). In vertebrates, many axons are surrounded by an insulating myelin sheath, which facilitates rapid impulse conduction. The axon terminal region, where contacts with other cells are made, displays a wide range of morphological specializations, depending on its target area in the central or peripheral nervous system. Classically, two major morphological types of contacts, or *synapses*, may be recognized by electron microscopy: the asymmetric synapses, responsible for transmission of excitatory inputs, and the symmetric or inhibitory synapses.

The cell body and the dendrites are the two major domains of the cell that receive inputs, and the dendrites play a critically important role in providing a massive receptive area on the neuronal surface. In addition, there is a characteristic shape for each dendritic arbor, which is used to classify neurons into morphological types. Both the structure of the den-

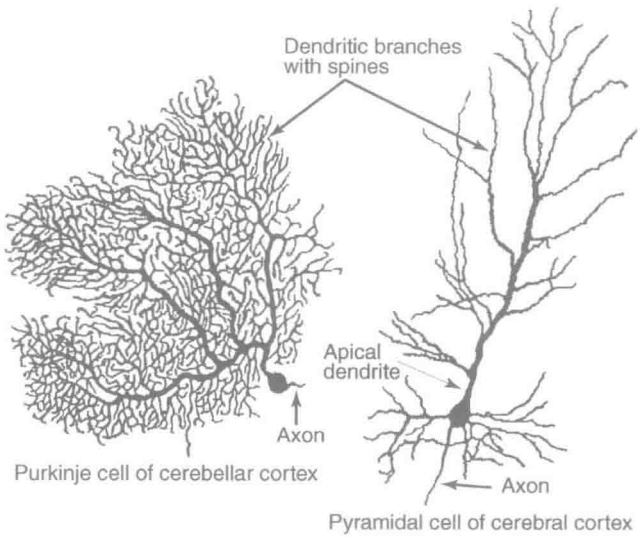

FIGURE 1.1 Typical morphology of projection neurons. On the left is a Purkinje cell of the cerebellar cortex, and on the right, a pyramidal neuron of the neocortex. These neurons are highly polarized. Each has an extensively branched, spiny apical dendrite, shorter basal dendrites, and a single axon emerging from the basal pole of the cell.

dritic arbor and the distribution of axonal terminal ramifications confer a high level of subcellular specificity in the localization of particular synaptic contacts on a given neuron. The three-dimensional distribution of the dendritic arborization is also important with respect to the type of information transferred to the neuron. A neuron with a dendritic tree restricted to a particular cortical layer may receive a very limited pool of afferents, whereas the widely expanded dendritic arborizations of a large pyramidal neuron will receive highly diversified inputs within the different cortical layers in which segments of the dendritic tree are present (Fig. 1.2) (Mountcastle, 1978; Peters and Jones, 1984; Schmitt *et al.*, 1981; Szentagothai and Arbib, 1974; Lund *et al.*, 1995; Björklund *et al.*, 1990). The structure of the dendritic tree is maintained by surface interactions between adhesion molecules and, intracellularly, by an array of cytoskeletal elements (microtubules, neurofilaments, and associated proteins), which also take part in the movement of organelles within the dendritic cytoplasm.

An important specialization of the dendritic arbor of certain neurons is the presence of large numbers of dendritic spines, which are membrane-limited organelles that project from the surface of the dendrites. They are abundant in large pyramidal neurons and are much sparser on the dendrites of interneurons. Spines are more numerous on the apical shafts of the pyramidal neurons than on the basal dendrites. As many as 30,000 to 40,000 spines are present on the largest pyramidal neurons. Spines constitute the region of the dendritic arborization that receives most of the excitatory input. Each spine generally contains one asymmetric synapse; thus, the approximate density of excitatory input on a neuron can be inferred from an estimate of its number of spines. The cytoplasm within the spines is characterized by the presence of polyribosomes and a variety of filaments, including actin and α- and β-tubulin, as well as a spine apparatus comprising cisternae, membrane vesicles, and stacks of dense lamellar material (see Box 1.1) (see (Berkley, 1896; Gray, 1959; Ramón y Cajal, 1955; Coss and Perkel, 1985; Scheibel and Scheibel, 1968; Steward and Falk, 1986; Zhang and Benson, 2000; Nimchinsky *et al.*, 2002).

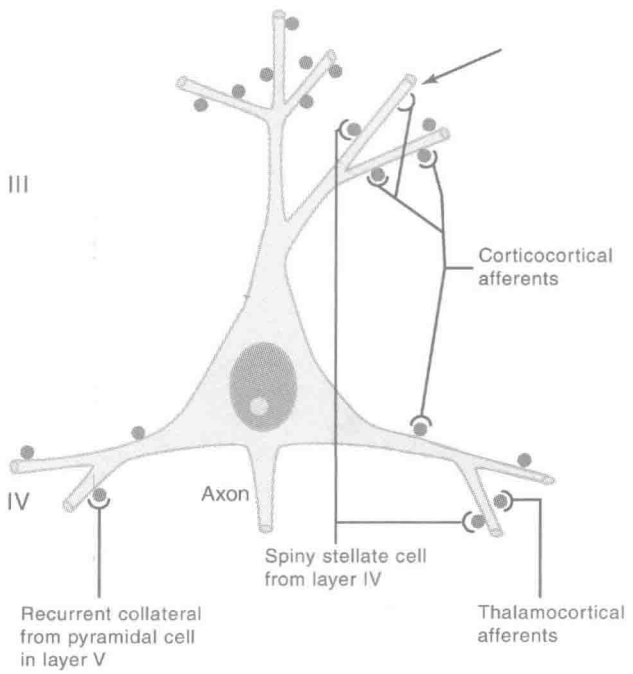

FIGURE 1.2 Schematic representation of four major excitatory inputs to pyramidal neurons. A pyramidal neuron in layer III is shown as an example. Note the preferential distribution of synaptic contacts on spines. Spines are labeled in red. Arrow shows a contact directly on the dendritic shaft.

The perikaryon contains the nucleus and a variety of cytoplasmic organelles. Stacks of rough endoplasmic reticulum are conspicuous in large neurons and, when interposed with arrays of free polyribosomes, are referred to as Nissl substance. Another feature of the perikaryal cytoplasm is the presence of a rich cytoskeleton composed primarily of neurofilaments and microtubules, discussed in detail in Chapter 2. These cytoskeletal elements are dispersed in "bundles" that extend into the axon and dendrites (Peters and Jones, 1984). Whereas the dendrites and the cell body can be characterized as the domains of the neuron that receive afferents, the axon, at the other pole of the neuron, is responsible for transmitting neural information. This information may be primary, in the case of a sensory receptor, or processed information that has already been modified through a series of integrative steps. The morphology of the axon and its course through the nervous system are correlated with the type of information processed by the particular neuron and by its connectivity patterns with other neurons. The axon leaves the cell body from a small swelling called the axon hillock. This structure is particularly apparent in large pyramidal neurons; in other cell types, the axon sometimes emerges from one of the main dendrites. At the axon hillock, microtubules are packed into bundles that enter the axon as parallel fascicles. The axon hillock is the part of the neuron from which the action potential is generated. The axon is generally unmyelinated in local-circuit neurons (such as inhibitory interneurons), but it is myelinated in neurons that furnish connections between different parts of the nervous system. Axons usually have larger numbers

BOX 1.1

SPINES

Spines are protrusions on the dendritic shafts of neurons and are the site of a large number of axonal contacts. The use of the silver impregnation techniques of Golgi or of the methylene blue used by Ehrlich in the late 19th century led to the discovery of spiny appendages on dendrites of a variety of neurons. The best known are those on pyramidal neurons and Purkinje cells, although spines occur on neuron types at all levels of the central nervous system. In 1896 Berkley observed that terminal boutons were closely apposed on spines (a fact that was later confirmed by Gray (1959) using electron microscopy) and suggested that spines may be involved in conducting impulses from neuron to neuron. In 1904, Santiago Ramón y Cajal suggested that spines could collect the electrical charge resulting from neuronal activity (Ramón y Cajal, 1955). He also noted that spines substantially increase the receptive surface of the dendritic arbor, which may represent an important factor in receiving the contacts made by the axonal terminals of other neurons. It has been calculated that the approximately 4000 spines of a pyramidal neuron account for more than 40% of its total surface area (Peters *et al.*, 1991).

More recent analyses of spine electrical properties have demonstrated that spines are dynamic structures that can regulate many neurochemical events related to synaptic transmission and modulate synaptic efficacy (Coss *et al.*, 1985) (see also Chapter 18). Spines are also known to undergo pathological alterations and have a reduced density in a number of experimental manipulations (such as deprivation of a sensory input) and in many developmental, neurological, and psychiatric conditions (such as dementing illnesses, chronic alcoholism, schizophrenia, and trisomy 21) (Scheibel and Scheibel, 1968). Morphologically, spines are characterized by a narrow portion emanating from the dendritic shaft, the neck, and an ovoid bulb or head. Spines have an average length of 2 μm despite considerable variability in morphology. At the ultrastructural level (Fig. 1.3), spines are characterized by the presence of asymmetric synapses and a few vesicles and contain fine and quite indistinct filaments. These filaments most likely consist of actin and α- and β-tubulins. The microtubules and neurofilaments present in the dendritic shafts do not penetrate the spines. Mitochondria and free ribosomes are infrequent, although many spines contain polyribosomes in their head and neck. Interestingly, most polyribosomes in dendrites are located at the bases of spines, where they are associated with endoplasmic reticulum, indicating that spines possess the machinery necessary for the local synthesis of proteins (Steward and Falk, 1986).

Another classic feature of the spine is the presence in the spine head of confluent tubular cisterns that represent an extension of the dendritic smooth endoplasmic reticulum. Those cisterns are referred to as the spine apparatus. The function of the spine apparatus is not fully understood but may be related to storage of calcium ions during synaptic transmission. For additional reviews on spines, see Zhang and Benson (2000) and Nimchinsky *et al.* (2002).

of neurofilaments than do dendrites, although this distinction can be difficult to make in small elements that contain fewer neurofilaments. In addition, the axon may be extremely ramified, as in certain local-circuit neurons; it may give out a large number of recurrent collaterals, as in neurons connecting different cortical regions; or it may be relatively straight in the case of projections to subcortical centers, as in cortical motor neurons that send their very long axons to the ventral horn of the spinal cord. At the interface of axon terminals with target cells are the synapses, which represent specialized zones of contact consisting of a presynaptic (axonal) element, a narrow synaptic cleft, and a postsynaptic element on a dendrite or perikaryon. We consider the fine structure of synapses later in this chapter. In the next section, we turn our attention to the principal morphological features of several neuronal types from the cerebral cortex, subcortical structures, and periphery as typical examples of the cellular diversity in the nervous system.

Pyramidal Cells Are the Main Excitatory Neurons in the Cerebral Cortex

All of the cortical output is mediated through pyramidal neurons, and the intrinsic activity of the neocortex can be viewed simply as a means of finely tuning their output. A pyramidal cell is a highly polarized neuron, with a major orientation axis per-

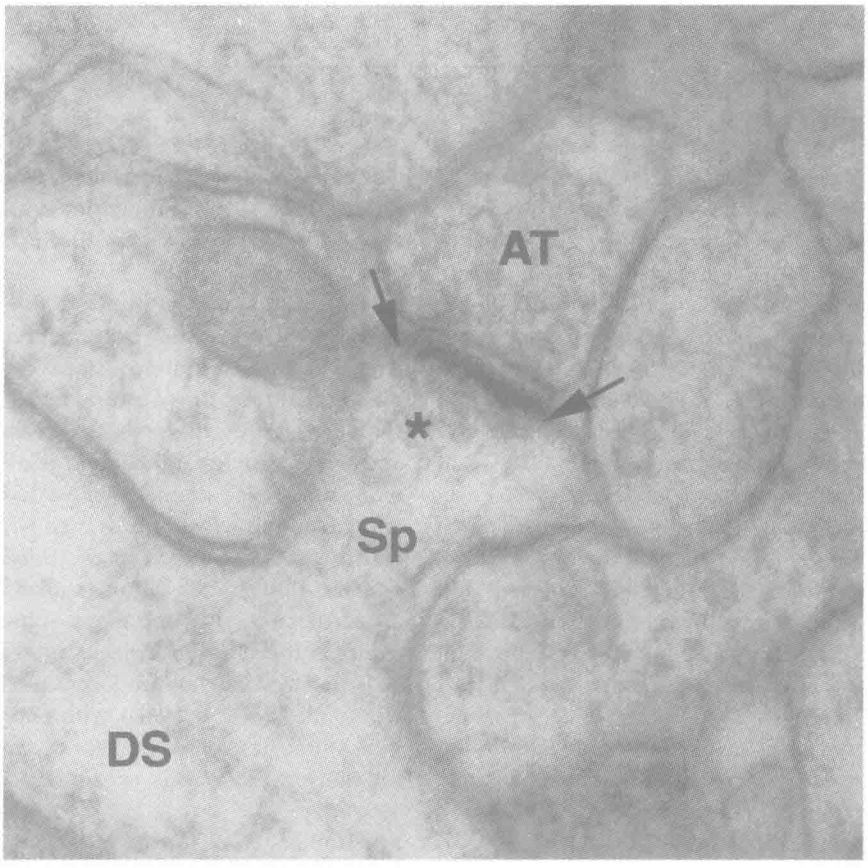

FIGURE 1.3 Ultrastructure of a single dendritic spine (Sp). Note the narrow neck emanating from the main dendritic shaft (DS) and the spine head containing filamentous material, the cisterns of the spine apparatus, and the postsynaptic density of an asymmetric synapse (arrows). AT, axon terminal.

pendicular (or orthogonal) to the pial surface of the cerebral cortex. In cross section, the cell body is roughly triangular (Fig. 1.2), although a large variety of morphological types exist with elongate, horizontal, or vertical fusiform or inverted perikaryal shapes. A pyramidal neuron typically has a large number of dendrites that emanate from the apex and form the base of the cell body. The span of the dendritic tree depends on the laminar localization of the cell body, but it may, as in giant pyramidal neurons, spread over several millimeters. The cell body and dendritic arborization may be restricted to a few layers or, in some cases, may span the entire cortical thickness (Jones, 1984).

In most cases, the axon of a large pyramidal cell extends from the base of the perikaryon and courses toward the subcortical white matter, giving off several collateral branches that are directed to cortical domains generally located within the vicinity of the cell of origin (as explained later in this section). Typically, a pyramidal cell has a large nucleus, a cytoplasmic rim that contains, particularly in large pyramidal cells, a collection of granular material chiefly composed of lipofuscin. The deposition of lipofuscin increases with age and is considered a benign change. Although all pyramidal cells possess these general features, they can also be subdivided into numerous classes based on their morphology, laminar location, and connectivity (Fig. 1.4) (Jones, 1975). For instance, small pyramidal neurons in layers II and III of the neocortex have restricted dendritic trees and form vast arrays of axonal collaterals with neighboring cortical domains, whereas medium-to-large pyramidal cells in deep layer III and layer V have much more extensive dendritic trees and furnish long corticocortical connections. Layer V also contains very large pyramidal neurons arranged in clusters or as isolated, somewhat regularly spaced elements. These neurons project to subcortical centers such as the basal ganglia, brainstem, and spinal cord. Finally, layer VI pyramidal cells exhibit a greater morphological variability than do pyramidal cells in other layers and are involved in certain corticocortical as well as corticothalamic projections (Feldman, 1984; Hof *et al.*, 1995a,b).

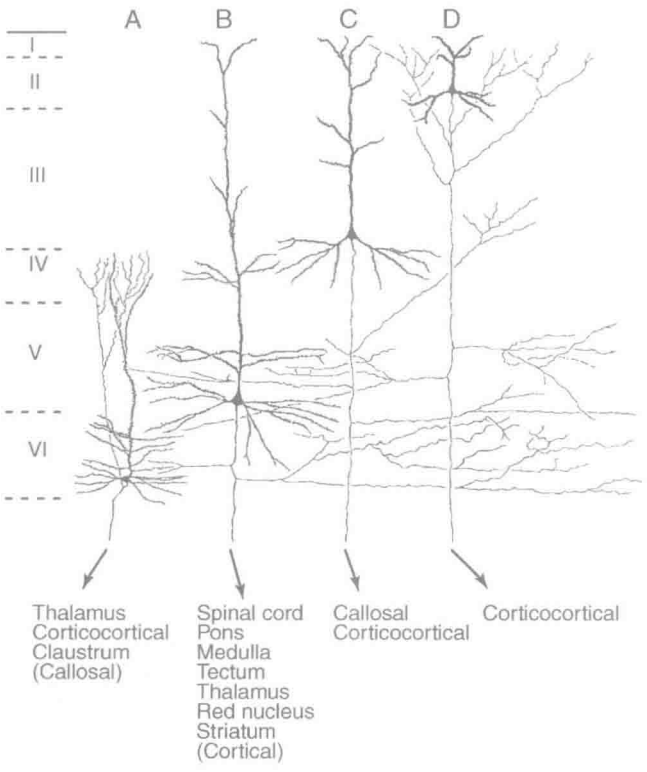

FIGURE 1.4 Morphology and distribution of neocortical pyramidal neurons. Note the variability in cell size and dendritic arborization as well as the presence of axon collaterals, depending on the laminar localization (I–VI) of the neuron. Also, different types of pyramidal neurons with a precise laminar distribution project to different regions of the brain. Adapted with permission, from Jones (1984).

The excitatory inputs to pyramidal neurons can be divided into intrinsic afferents, such as recurrent collaterals from other pyramidal cells and excitatory interneurons, and extrinsic afferents of thalamic and cortical origin. The neurotransmitters in these excitatory inputs are thought to be glutamate and possibly aspartate. Although this division may appear relatively simplistic, the complexity and heterogeneity of excitatory transmission in the neocortex may not be derived from the presynaptic side, but rather from the postsynaptic side of the synapse. In other words, at the molecular level, a variety of glutamate receptor subunit combinations may confer different functional capacities on a given glutamatergic synapse (see Chapter 11).

Pyramidal cells not only furnish the major excitatory output of the neocortex, but also act as a major intrinsic excitatory input through axonal collaterals. The collaterals of the main axonal branch that exits from the cortex are referred to as recurrent collaterals because they ascend back to superficial layers; thus, the collateral branches of a pyramidal cell synapse in layers superficial to their origin, although a deep or local system of branches is also present (see Fig. 1.4). Although many of these branches ascend in a radial, vertical pattern of arborization, there are a separate set of projections that travel horizontally over long distances (in some instances as much as 7–8 mm). One of the major functions of the vertically oriented component of the recurrent collaterals may be to interconnect layers III and V, the two major output layers of the neocortex. In layer III pyramidal cells, 95% of the synaptic targets of the recurrent cells are other pyramidal cells. This is true of both the vertical and the distant horizontal recurrent projections. In addition, the majority of these synapses are on dendritic spines and, to some degree, on dendritic shafts. It is possible that there are regional and laminar specificities to these synaptic arrangements, although such fine patterns are not yet fully elucidated (Schmitt *et al.*, 1981; Szentagothai and Arbib, 1974; Lund *et al.*, 1995; Kisvarday *et al.*, 1986a,b). These recurrent projections function to set up local excitatory patterns and coordinate multineuronal assemblies into an excitatory output.

Spiny Stellate Cells Are Excitatory Interneurons

The other major excitatory input to pyramidal cells of cortical origin is provided by the interneuron class referred to as spiny stellate cells, small multipolar neurons with local dendritic and axonal arborizations. These neurons resemble pyramidal cells in that they are the only other cortical neurons with large numbers of dendritic spines, but they differ from pyramidal neurons in that they lack an apical dendrite. Although the dendritic arbor of these neurons tends to be local, it can vary from a primarily radial orientation to one that is more horizontal. The relatively restricted dendritic arbor of these neurons is presumably a manifestation of the fact that they are high-resolution neurons that gather afferents to a very restricted region of cortex. The dendrites rarely leave the layer in which the cell body resides. The spiny stellate cell also resembles the pyramidal cell in that it provides asymmetric synapses that are presumed to be excitatory, and, like pyramidal cells, these neurons are thought to use either glutamate or aspartate as their neurotransmitter.

Spiny stellate cells exhibit extensive regional and laminar specificities in their distribution. Spiny stellate cells are found in highest concentration in layers IVC and IVA of the primary visual cortex, where they constitute the predominant neuronal type. They are also found in large numbers in layer IV of other