In: Encyclopedia of Learning and Memory. Edited by L.R. Squire. Macmillan Publishing Company, New York. 1992. pp. 219-225.

Neuron

Cells of the central nervous system are divided into two categories, neurons and glial cells. The present paper deals with the characteristics of neurons in the vertebrate central nervous system. Neurons are independent morphological, trophic, and functional entities: they develop from the *neural plate of the ectoderm.* They differ from glial cells in their ability to generate propagated *action potentials* (spikes), in the release of neuroactive substances called *neurotransmitters,* and in their ability to communicate with other cells through specialized membrane junctions called *synapses.* There was a long debate in the first half of the twentieth century between those who maintained that the brain was a continuous reticulum of fibers and those who proposed that elements of the nervous system were discrete cells (for a historical account see Peters, Palay, and Webster, 1991). The first electron microscopic studies decisively resolved the issue by showing that each neuron is delineated by a continuous *plasma membrane* and is separated from other cells by a gap. However, like other cells of the body, neurons in some parts of the nervous system are interconnected through continuous cytoplasmic bridges organized into *gap junctions* that are permeable to ions and small molecules.

Neurons are polarized cells receiving information at certain locations on their plasma membrane and releasing neurotransmitters to other cells, usually from other sites (Kandel and Schwartz, 1985; Peters, Palay, and Webster, 1991; Shepherd, 1990). They emit several processes originating from the *cell body* or *soma.* One (occasionally two or three) of the processes is an *axon* propagating the action potential to the transmitter-releasing nerve terminals. The other processes are called *dendrites* and are usually shorter and branch less frequently than the axon. The shape and three-dimensional distribution of the processes are characteristic for each category of neuron and reflect their connections with other cells and, ultimately, the neuron's place in the neuronal network. The general arrangement is that information arrives through afferent (i.e., inward—transmitting) synapses on the dendritic processes and the cell body, and is transmitted to other cells through axonal enlargements, also called *boutons,* present on the axonal arborization. However, significant exceptions to this rule occur in some parts of the brain (see below). Neurons in invertebrates usually have only one process originating from the cell body that gives rise to branches, all of them both receiving and giving information and involved in different operations.

The Soma

The soma has a diameter of 5–50 microns and contains the nucleus and the usual cell organelles present in most cells, with great similarity to those present in secretory cells. This is in line with the observation that most neurons secrete proteins and peptides in addition to small transmitter molecules. For example, the rough endoplasmic reticulum (ER), the site of protein synthesis, is often highly developed and is organized into parallel lamellae forming large *Nissl bodies.* The *Golgi apparatus* is similarly highly developed and often extends into the proximal dendritic processes, which also contain ER and ribosomes. The axons are usually devoid of ribosomes and, together with the nerve terminals, lack the ability for significant protein synthesis. Thus the neuron is also a polarized biochemical machine where protein and other components synthesized in the cell body are transported through the axon to the nerve terminals.

The transport of molecules and organelles between the processes and the soma is bidirectional and is supported by the cytoskeleton, which also maintains the shape of the processes (see Kandel and Schwartz, 1985). The cytoskeleton consists of *microtubules* (polymers of *tubulin* dimers, external diameter 25–28 nanometers), *neurofilaments* (polymers of *cytokeratins,* diameter 10 nanometers), and *microfilaments* (polymers of *actin,* diameter 5–7 nanometers).

In addition to rough ER, many neurons are rich in smooth ER that is involved in intracellular Ca_2^+ storage and release. Cysternae of the ER are often closely aligned with the plasma membrane of both the soma and dendrites forming *subsurface cysternae.*

Lysosomes are found in all neurons. Secondary lysosomes accumulate throughout the life of the

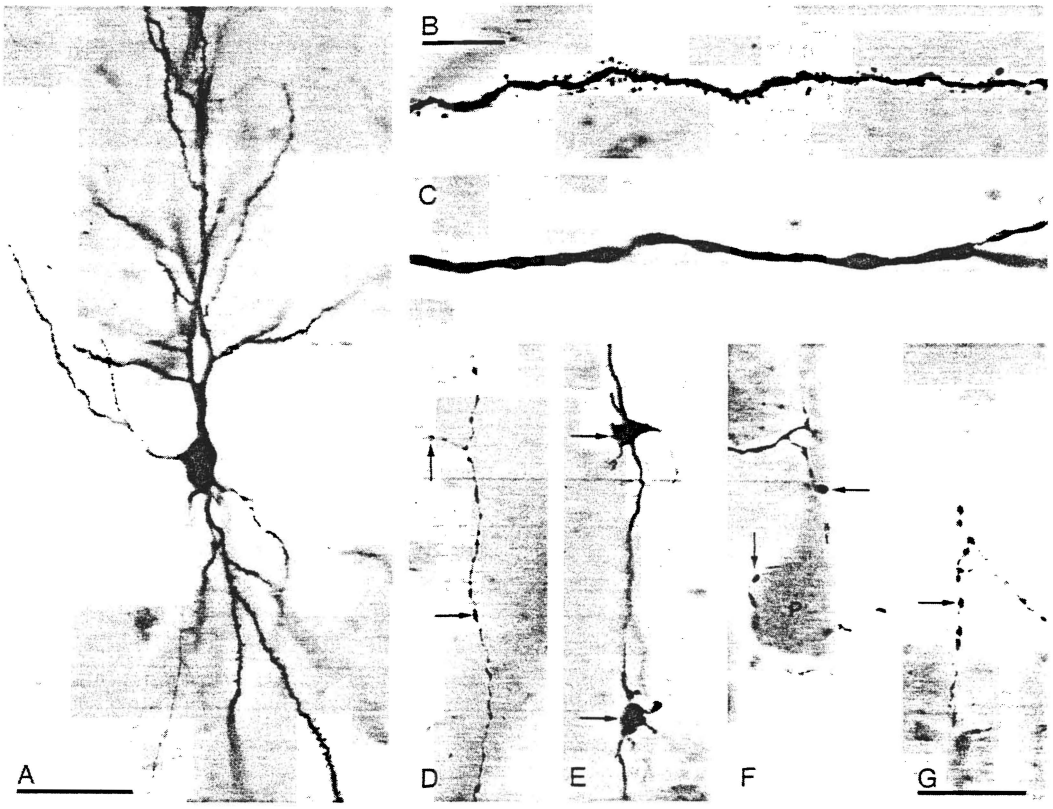

Figure 1. Parts of different neurons in the rat hippocampus shown in light microscopic photographs. The hippocampal formation is involved in memory formation. All cells were marked by intracellular injection of a marker molecule through a fine glass micropipette. The marker was transported to all the processes of the living cells. *Z.-S. Han, E. Buhl, and P. Somogyi, unpublished material.*

A. *Pyramidal cell* in the CA1 region emitting dendrites into two different layers toward the top and bottom of the picture; the two sets of dendrites sample different inputs coming from different sources. The light band in the middle contains the cell bodies of many more unmarked pyramidal cells. The rightmost dendrite is shown at higher magnification (rotated) in B, illustrating the large number of dendritic spines typical of these cells. C. Another type of cell, the *basket cell,* which has its cell body and dendrites in the same layers as the pyramidal cells, has smooth dendrites. Such dendrites have integrative properties different from spiny dendrites.

D–G. Terminal axonal segments of four different neuronal types, showing the differences in transmitter-releasing terminals (arrows) reflecting the specializations in synaptic connections. D. Axon collateral of a CA1 *pyramidal cell* similar to that shown in A. E. Two terminals of a mossy fiber originating from a *granule cell* in the dentate gyrus and making synapses with the apical dendrites of hippocampal pyramidal cells (not marked). F. Terminals of a *basket cell* surround the cell body and the main apical dendrite of a pyramidal cell (P), seen as a pale silhouette. G. The vertically aligned boutons of a *chandelier cell* form multiple synaptic contacts with the axon initial segment (not marked) of a pyramidal cell. Basket and chandelier cells release the inhibitory neurotransmitter GABA, but to different parts of the same postsynaptic cell. The pyramidal and granule cell terminals release the excitatory amino acid glutamate.

Scales: A, 50 microns; B and C, 10 microns; D–G, 20 microns.

cell and coalesce into *lipofuscin granules* showing characteristic distribution for each neuronal type.

The Dendrites

The dendrites are rarely longer than 1 millimeter and can be as short as 10–50 microns with a diameter of 3–0.05 microns, tapering toward their tip and decreasing in diameter at branching points. The main criterion that differentiates them from the axon is that dendrites lack the morphologically distinct initial segment (see below) at their origin from the soma. With the exception of peripheral sensory neurons, all neurons have dendrites. They are generally postsynaptic to axon terminals; from scores to tens of thousands of synapses converge on the dendritic tree of a single neuron.

In some parts of the nervous system, most prominently in the retina (amacrine cells), the olfactory bulb, the thalamus, the substantia gelatinosa of the brain stem and spinal cord, and the superior colliculus, dendrites of some classes of cells can be both pre- and postsynaptic. In these cases the dendrite at the presynaptic site contains synaptic vesicles and presynaptic membrane specialization as well as nearby postsynaptic membrane specializations at synapses received by the neuron. Often these combined pre- and postsynaptic sites are located on protrusions, grapelike clusters or gemmules, isolating the formations from each other on the same cell, and providing a basis for independent action. Synapses between two dendrites can be reciprocal, each partner receiving as well as giving synapses to the other at closely located sites.

Dendrites have various short postsynaptic extrusions, the best-known of them being *dendritic spines* (Figure 1). Spines are particularly prominent and numerous on cortical pyramidal and spiny stellate cells, on Purkinje cells, and on the spiny neurons of the neostriatum. Spines frequently contain a specialized organelle, the spine apparatus, consisting of parallel membrane saccules and continuous with the smooth ER of the dendritic shaft. The spine apparatus is thought to be involved in Ca^{2+} sequestration. Spines usually receive excitatory synaptic input and occasionally an additional inhibitory input. Numerous theories have been put forward for the role of spines. Of these, the formation of a biochemical compartment, semi-independent from the dendritic shaft and from other spines, seems the most attractive. The integrative properties of dendrites are determined by (1) their shape; (2) their intrinsic membrane properties, underlined by the presence and distribution of different *ion channels;* and (3) the location of synaptic inputs and their relationship to other inputs (for more detail, see Shepherd, 1990).

In addition to receiving and sometimes giving synaptic junctions, dendrites can also be connected to other dendrites and nerve terminals through small cytoplasmic bridges forming *gap junctions.* Gap junctions are sites of electrotonic transmission because they are permeable to ions and can facilitate the synchronization of neurons.

The Axon

Most neurons have axons; the few exceptions are retinal amacrine cells and granule cells of the olfactory bulb (Shepherd, 1990). Axons usually originate from the soma, rarely from a major dendrite, and begin with the axon hillock. A specialized trilaminar inner coat of the membrane, recognizable with the electron microscope, identifies the *axon initial segment,* which has the highest density of voltage-sensitive sodium channels. It is thought to be the site of the generation of the propagated action potential. Similar membrane undercoating is found in the axon at *nodes of Ranvier* between myelin segments. The other unique feature of the initial segment is the presence of interconnected microtubules organized into fascicles. In some regions of the brain the axon initial segment can receive numerous synapses. Such synapses are provided by the *chandelier cell,* a specialized inhibitory neuron unique to cortex, which makes synapses exclusively on the axon initial segment of pyramidal and spiny stellate neurons (Figure 2). Most axons emit several collaterals along their course addressing particular brain areas or groups of cells in the same brain area (Figure 3).

Myelin Sheath

The axons of neurons in the brain can be myelinated for part or for the whole of their course, or can be completely unmyelinated (Peters, Palay, and Webster, 1991). Some types of neurons, such as corticospinal cells and Purkinje cells, always have myelinated axons. The myelin is segmented, and each segment is formed by the plasma membrane of an *oligodendroglial cell.* Segments are

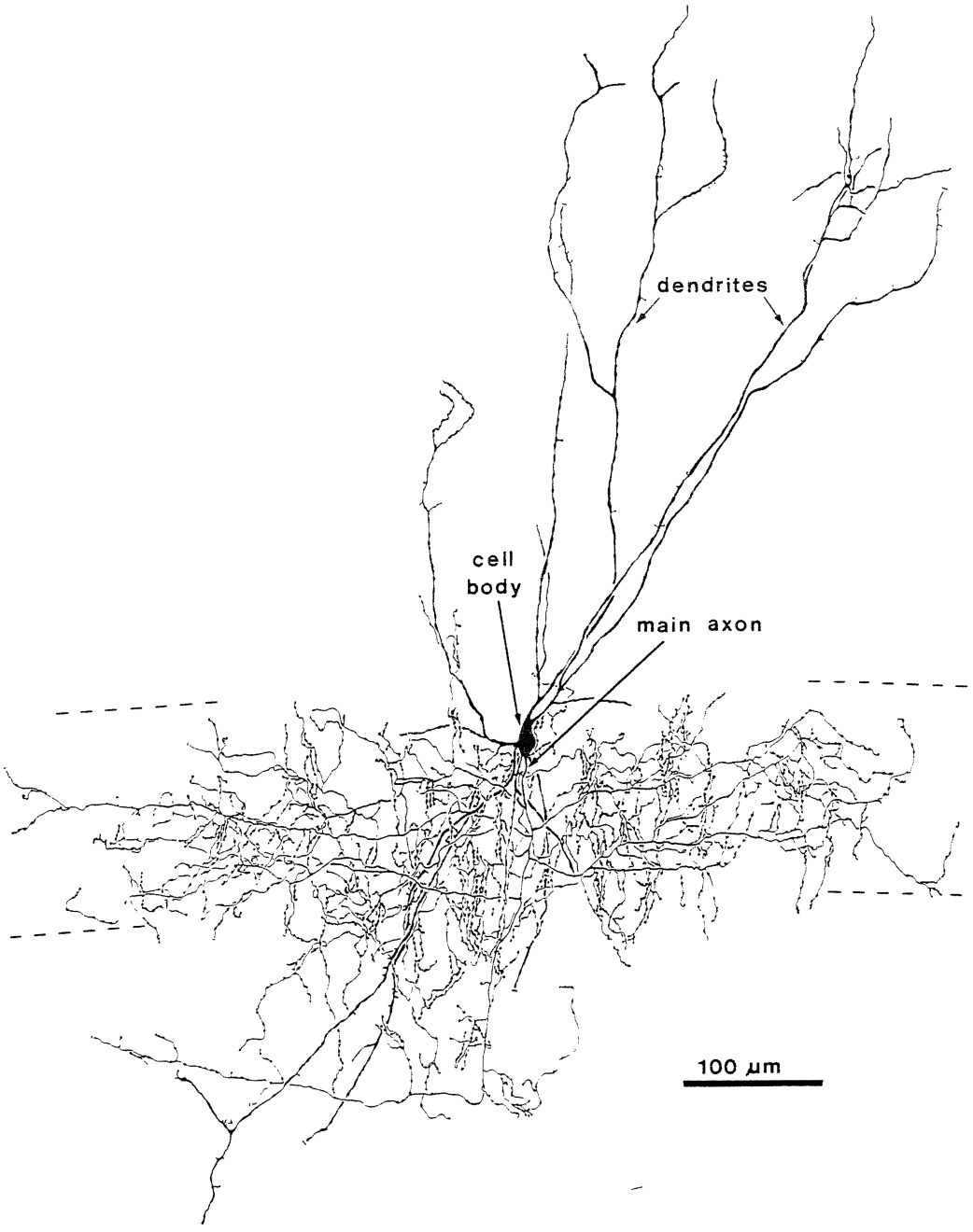

Figure 2. Tracing of the processes of a local circuit inhibitory neuron, the *chandelier cell,* from the hippocampus of the cat. The terminals of this cell make synapses exclusively with the axon initial segment of pyramidal cells; therefore, the axon is localized mainly to the layer of pyramidal cell bodies enclosed by broken lines. Each vertically oriented terminal axon segment targets one initial segment; thus from this partial reconstruction it can be established that this single chandelier cell makes synapses with at least 320 pyramidal cells. The dendrites of the cell occupy the same layers as the pyramidal cell dendrites, so the cell has access to all the information pyramidal cells receive. The cell was visualized by Golgi impregnation. *Based on data in Somogyi et al., 1985.*

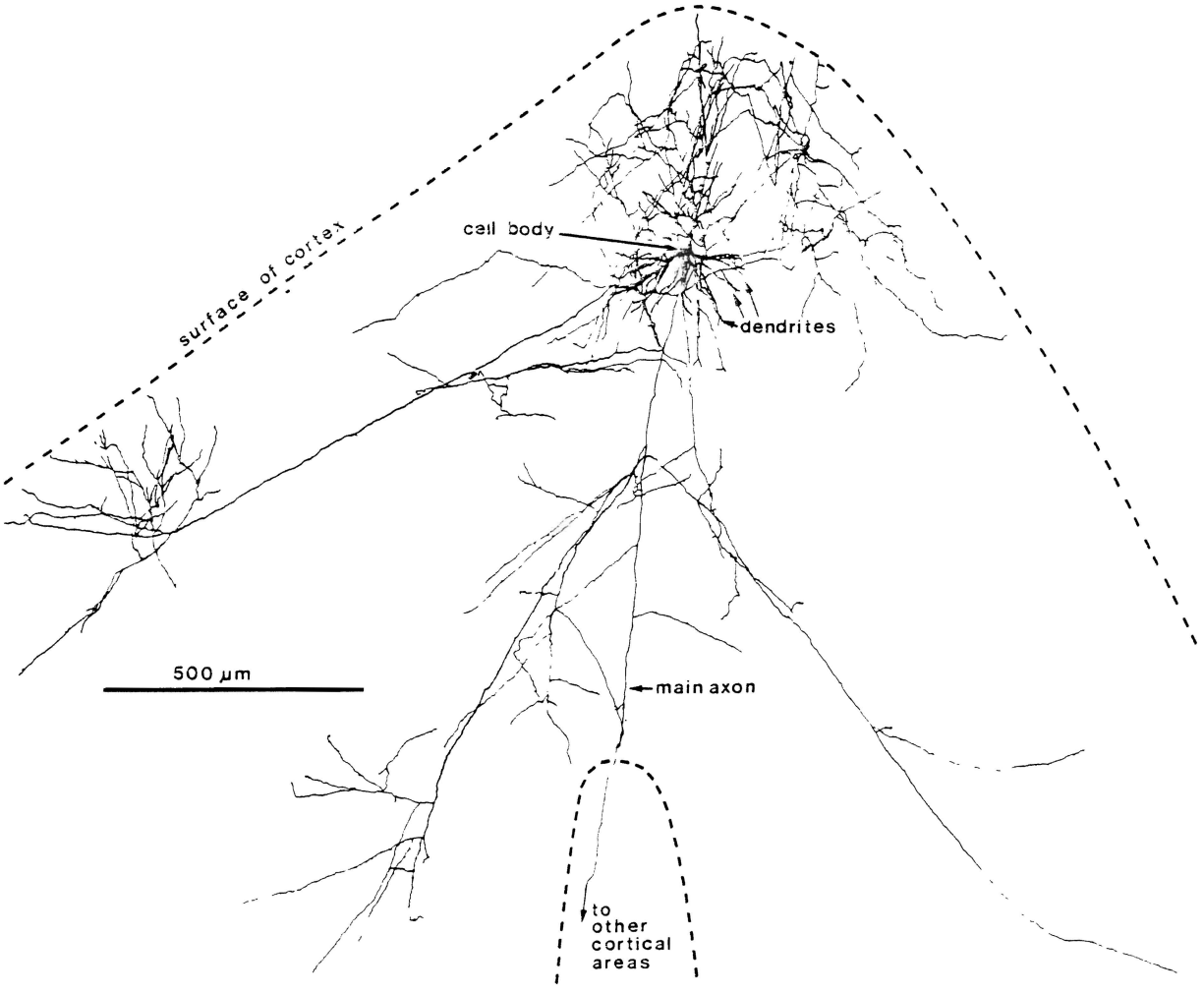

Figure 3. Tracing of the processes of a *pyramidal cell* in the visual cortex of cat. The cell body is in the superficial layer and emits dendrites reaching a few hundred microns. The main axon descends to the white matter (lower broken line) and proceeds to innervate other cortical areas. On its way through the gray matter it gives rise to several axon collaterals traveling for several millimeters within the same cortical area and addressing groups of cells with local ramifications while ignoring other groups of cells. The axon also richly supplies neurons in the vicinity of the cell body. Such selective connections enable effective coordination of neurons with similar properties. Having both a local axon arborization and a distant one gives the neuron both a local circuit role and a role in connecting different areas of the brain. The cell was visualized by the intracellular injection of a marker molecule. *Based on data from Kisvarday et al., 1986.*

interrupted by nodes of Ranvier, where axon collaterals often originate. The axons may acquire myelin for part of their course as they traverse a particularly heavily myelinated part of the brain. Axons may contain synaptic vesicles at nodes of Ranvier, and they may be presynaptic to neighboring dendrites.

Nerve Terminals

The terminal axon arborizations are characteristic of each cell type. The transmitter-releasing sites are bulbs or varicose enlargements having a diameter usually of 0.5–3 microns; they may have a position on the end of axon branches as *boutons termi-*

naux, or may be varicosities along the axon forming *boutons en passant* (Figure 1D–G). Many terminal boutons sit on the ends of short stalks branching off from main axon collaterals (Figure 1D, vertical arrow). Specialized formations of nerve terminals evolved, such as large mossy fiber terminals providing multiple localized input to the same target (Figure 1E), and climbing fibers providing multiple synapses distributed over the postsynaptic dendritic tree of the same target dendrite or cell. Boutons form *synaptic junctions* (see "Synapse" below). Boutons are usually only presynaptic to other cells, but terminals of a few cell types, most prominently the primary sensory afferents in the brain stem and spinal cord, may receive synapses and are postsynaptic to inhibitory terminals. One bouton may make synaptic junctions with only one postsynaptic element or may provide input to up to about ten different postsynaptic targets originating from about the same number of individual neurons. In some cases almost every bouton of the same axon establishes synapses with a different cell, providing a large degree of divergence in information transfer. Cortical cells, for example, may make synapses with thousands of other cortical neurons in a given area (Figure 3).

The boutons contain *synaptic vesicles*, which are membrane-delineated discrete structures. The morphology of the vesicles is characteristic to cell types and to some degree correlates with the chemistry of their neurotransmitter content. The two most common families of vesicles are the *small clear vesicles* with a diameter of 30–50 nanometers and the *large granulated vesicles* with a fine electron dense core and a diameter of about 80–200 nanometers. Boutons are also rich in mitochondria.

The synaptic vesicle–containing varicosities of some neurons do not establish morphologically recognizable synaptic junctions at all of their boutons. This applies in particular to neurons that use monoamines as transmitters.

Analysis of Neuronal Circuits

Connectivity patterns of morphologically identified neurons can be traced via the transport of marker molecules through the processes (see Heimer and Zaborszky, 1989). The active transport in the living cell can be exploited by introducing suitable tracers into the neuron that are carried to the dendritic and axonal processes (Figures 1, 3). Tracer molecules can be introduced directly into the cell or into the surrounding extracellular space from which the cell can take them up by an active process. It is also possible to label the processes of neurons that have been fixed with chemical agents (Figure 2). The visualization of processes makes it possible to identify the connections of particular types of neurons in the same area of the brain or between different brain regions. The morphological appearance of neurons reflects their patterns of connections. In many cases synapses from a given source terminate on certain parts of the neuron because the operation that the given input provides is best carried out in that part of the cell (Figures 1E–G, 2). Homologous parts of numerous postsynaptic cells in a given area of the brain tend to align with inputs arriving at that part of the cell, and this leads to the development of laminated structures. For example, axons originating from the CA3 region of the hippocampus terminate mainly on the main *apical dendrites* of pyramidal cells in the CA1 region, and the local recurrent collaterals of pyramidal cells in the CA1 sector address the *basal dendritic* region of the pyramidal cells (Figure 1A). The separation of inputs and the minimum amount of axon necessary to achieve addressing is ensured by the alignment of pyramidal cells.

The terminals of some neurons are all localized in the same brain area where the cell body is located. These cells play a role in the local processing of information and are called *local circuit neurons* (Figure 2). Other cells connect different brain regions or supply the periphery with their axons; these are called *projection neurons*. Many projection neurons also have axon collaterals within the same brain area where the cell is located, and thus play both a local circuit and a projection role (Figure 3). Accurate knowledge of the connectivity, especially in quantitative terms, is a prerequisite of establishing the operations taking place in real neural networks.

(See also MEMBRANE CHANNELS AND THEIR MODULATION IN LEARNING AND MEMORY; NEUROTRANSMITTER SYSTEMS AND MEMORY.)

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