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Dendrite structure

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Summary

Dendrites extend from the cell body of the neuron and are specialized for processing synaptic information. Dendritic arbors assume diverse forms branching in characteristic spatial domains where they receive specific synaptic inputs. Synaptic inputs occur directly on the shaft of some dendrites, but other dendrites have dendritic spines or specialized enlargements that host synapses. These specializations also occur in many different forms related both to local connectivity and the need for compartmentalization of molecular signaling. The use of three dimensional reconstructions from serial section electron microscopy (3DEM) has shown that these dendritic synaptic specializations differ widely in dimensions, distribution, and intracellular composition. The shape and composition of dendrites and their synaptic specializations are influenced throughout life by genes, environment, learning, memory, and neuropathological conditions. Therefore, understanding dendrite structure is essential to understanding dendrite function.

Introduction

What is the purpose of dendrites? How are their diverse shapes related to neuronal function? Why are specialized compartments formed at the sites of synaptic contacts? The Spanish neuroanatomist Santiago Ramón y Cajal posed and to a remarkable extent answered these questions more than a 100 years ago, summarized in his compendium *Histology of the Nervous System* (Ramon Y Cajal, 1995). Ramón y Cajal used a variety of experimental approaches, especially the technique developed by the Italian neuroanatomist, Camilo Golgi, to stain individual neurons. From this work, Ramón y Cajal proposed that axons and dendrites do not anastomose in continuity between different neurons (Ramon Y Cajal, 1954) as was originally proposed by Golgi (Golgi, 1908). The importance of the Golgi technique together with Ramón y Cajal's astute analyses won them the Nobel Prize in Physiology or Medicine in 1906 (Shepherd, 1991). Their Norwegian contemporary, Fridtjof Nansen, took a comparative approach, also using the Golgi technique to study nervous system structure in diverse organisms from crayfish to hagfish and mammals, to establish that the complexity of the dendritic processes and the so-called "dotted substance" (neuropil), where axons and dendrites communicate, is "more complicated and extensive the higher an animal is mentally

developed" (Fridtjof Nansen, 1887). Similarly, Ramón y Cajal argued that phylogenetic differences in specific neuronal morphologies support the relationship between dendritic complexity and the number of connections. For example, the complexity of dendritic arbors increases with increasingly complex nervous systems on different types of vertebrate neurons, including cerebellar Purkinje cells, cortical pyramidal cells, and mitral cells of the olfactory bulb. (See Chapter 2 for more phylogenetic differences.) Although the work of Ramón y Cajal favored what became known as the neuron doctrine, namely that communication occurred at junctions between discrete neurons, proof awaited the advent of the electron microscope and demonstration of a synaptic cleft between the presynaptic axon and postsynaptic dendrite (Palade and Palay, 1954; De Robertis and Bennett, 1955).

Modern approaches to evaluate dendritic, axonal, and glial properties provide reasons to reconsider the strictly uni-directional, axo-dendritic patterns of synaptic activation championed in the original neuron doctrine (Shepherd, 1991; Guillery, 2005; Kruger and Otis, 2007). As Ramón y Cajal and Nansen correctly surmised, dendrites usually comprise the receptive surfaces of a neuron, while axons usually deliver signals from other neurons. However, dendrites can also be output devices. For example, dendrites make reciprocal synapses having both pre- and postsynaptic components on the corresponding pairs of dendrites in the retina, olfactory bulb, lateral geniculate nucleus, some cortical neurons and some peripheral sensory neurons (Price and Powell, 1970; Lieberman, 1973; Sloper and Powell, 1978; Ellias and Stevens, 1980). Conversely, axons also provide receptive surfaces, making axo-axonic synapses in many places throughout nervous systems (Cuello, 1983). Furthermore, dendrites, axons, and glia all form gap junctions, which are bidirectional sites of communication through channels that are arranged so as to span the adjacent membranes and bridge the extracellular space (Bennett and Zukin, 2004). While such dendro-dendritic, axo-axonic, and gap junction-mediated communication is relatively rare compared to axo-dendritic, they nevertheless play important roles in both direct neuron-to-neuron communication and modulation of this communication.

Dendritic arbors with greater complexity have the potential to host more synapses. Consider that a neuron with a roughly spherical cell body has a very limited surface area for receiving inputs. By extending dendrites, the neuron increases the surface area without excessively increasing cell volume. For example, the dendrites of cat spinal motoneurons occupy a volume of 300,000 μm^3 and provide 370,000 μm^2 of surface area for synaptic input (Ulfhake and Kellerth, 1981). To provide an equivalent surface area, a spherical cell body would have to be 342 μm in diameter and occupy more than 20,900,000 μm^3 in volume, a factor of 70 greater than dendrite-bearing motoneurons.

The convolution of the cell surface into a dendritic arbor also facilitates the packing of a larger number of neurons in close proximity and extends their reach to more axons. However, the expanded dendritic arbor does not necessarily translate with one-to-one correspondence to increased synapse density. For example, the fraction of axons within reach or touching a hippocampal pyramidal cell dendrite that actually form synapses on that dendrite is only about 20%; furthermore, the surface area occupied by those synapses is only about 10% (Harris and Stevens, 1988a; Harris and Stevens, 1989;

Mishchenko et al., 2010). These modern 3DEM findings suggest that enhancing synaptic connectivity (Peters and Kaiserman-Abramof, 1970; Swindale, 1981; Gray, 1982) is probably not the primary function of dendrites, their spines, and other synaptic specializations.

Dendrites make relatively local connections as compared with the axon. The axon, emerging either from the soma or a proximal dendrite, may extend to distant targets a meter or more away from the cell body (e.g. motor neurons and corticospinal projection neurons). In contrast, dendrites are rarely longer than 1-2 mm, even on the largest neurons, and are often much smaller (Table 1.1). The diameter of dendrites at their origin from the cell body is proportional to the diameter of the cell body. Dendrites taper and ramify in proportion to their size, such that the total length and number of branches are also correlated with dendrite caliber. Thus, larger neurons typically have both larger cell bodies and more extensive dendritic fields. Compare and contrast, for example, the Purkinje dendritic arbor that integrates input from multiple cell types with the tiny granule cell that typically forms just 4 small dendritic branches, each ending in a claw that forms synapses (Fig 1.1).

In this chapter we consider the functional significance of diversity in the structure of dendritic arbors together with diversity in the structure and subcellular composition of individual dendrites, dendritic spines, and other synaptic specializations. We show that dendrites contain subcellular structures including smooth endoplasmic reticulum, microtubules, endosomes, Golgi apparatus, polyribosomes, and others that can rapidly direct resources to sites of synaptic activation and plasticity. We end with an analysis of ultrastructural changes that occur in synaptic specializations during long-term potentiation, a cellular mechanism of learning, and various neuropathological conditions.

Dendrite Arbors

Both the geometry (Fig. 1.2, Table 1.2) and density of dendritic branching (Figs. 1.2 and 1.3) define the dendritic arbor and are important for understanding connectivity in the nervous system. Dendritic arbors are shaped to receive inputs in particular spatial domains. At one extreme, a dendritic arbor connects a single remote target to the rest of the neuron, providing a highly *selective* arborization. At the other extreme, dendritic branches occupy most of the domain in a *space-filling* arborization. The majority of dendritic arborizations lie between these extremes and are considered to be *sampling* arborizations. Here we describe various geometrical patterns as a basis for understanding the consequences of diversity in dendritic arborization on synaptic connectivity.

Adendritic neurons have no dendrites and they usually have a single branched axon arising from the soma (Table 1.2). Examples of adendritic neurons occur in the trigeminal, nodose, and dorsal root ganglia. These neurons conduct sensory input from the periphery to the central nervous system. Although GABAergic and glutamatergic axons have been found to surround the soma of these adendritic neurons (Sholl, 1953; Sholl, 1967; Stoyanova et al., 1998), to our knowledge no electron microscopy studies

have been done to determine whether these processes make synapses on them.

Dendritic arbors of many slender neurons found throughout the brain have a *spindle radiation*, with two sparsely-branching dendrites emerging from opposite poles of the soma. Examples include the Lugaro cell of the cerebellar cortex (Palay and Chan-Palay, 1974) and bipolar cells of the cerebral cortex which are usually interneurons expressing calretinin in combination with neuropeptides (Cauli et al., 2014). This arborization would perform sparse sampling of two distinct input domains.

Stellate neurons of the central nervous system have a dendritic arbor with a *spherical or partial spherical radiation* depending on their position with respect to the boundaries of the region in which they reside. The dendrites of the cerebellar granule cells have spherical radiations that make synapses selectively at their claw-like ends (Fig. 1.1, above). Other examples include spinal cord neurons and principal neurons in non-laminated nuclei such as the inferior olive, pontine nuclei, striatum, and thalamus. Interneurons are defined as having axons that terminate locally within a particular brain region, and many interneurons have dendritic arbors with spherical radiations. Although attempts have been made to describe the variety of stellate arbor types in general terms (Ramón-Moliner, 1968), classification often comes down to individual characteristics. For example, in the ventral cochlear nucleus, descriptive morphologies of the dendritic arbor include spherical bushy, globular bushy, stellate, bushy multipolar, elongate, octopus, and giant (Ostapoff et al., 1994). These descriptors are not readily applicable to stellate neurons in other areas of the brain where, for example, in the cerebral cortex the primary distinguishing characteristic of the many stellate interneurons is not their dendritic arbors but rather the pattern of their axonal arborization (Jones, 1975). Overall, the morphology of stellate dendritic arbors suggests they perform selective or sparse sampling of axonal inputs that congregate locally within the neuropil of a circumscribed region.

Dendritic arbors with a *laminar radiation* spread in arbitrary directions from the cell body but are restricted to a *planar* region as seen, for example, in horizontal cells of the retina (Kolb et al., 1994) and in some interneurons of the hippocampus (Parra et al., 1998). Nearly 20 kinds of retinal ganglion cells are distinguished by their planar dendritic arborization patterns that are *offset* by one or more dendritic stems (Fukuda et al., 1984; Sterling, 1990; Wingate et al., 1992). These dendrites can ramify into one or more layers to access multiple types of afferent and provide either a selective or sampling arborization that gives rise to distinct physiological functions.

Multi-laminar radiation characterizes dendritic arborizations of retinal amacrine cells. At least 26 different types of amacrine cells can be identified based on their dendritic arborization and retinal tiling patterns alone (Mariani, 1990; Kolb et al., 1992; MacNeil and Masland, 1998). As with ganglion cells, the morphological differences in the extent of amacrine cell dendritic arbors also denote differences in the computational properties of these neurons.

Some dendritic arbors have a strictly *cylindrical radiation.* For example, in the globus pallidus of primates, the dendrites of the large pallidal neurons have a cylindrical radiation that fills spatial domains approximately 1000-1500 μm in diameter and 250 μm thick (Yelnik et al., 1984). These dendrites run parallel to the boundaries of the globus pallidus and thus perpendicular to incoming striatal axons such that each

neuron receives a broad distribution of input in their dense-sampling to space-filling arbors.

Many granule cell types have a dendritic arbor with a *conical radiation*, where the dendrites radiate from one side of the neuron in a cone or paraboloid fashion. This selective but dense sampling pattern characterizes granule cells in the hippocampal dentate gyrus, for example, where axonal input is strictly laminated with the primary excitatory input from the lateral entorhinal cortex synapses in the outer third, from the medial entorhinal cortex synapsing in the middle third, and the contralateral hippocampus inner third of the dendritic arbor.

The dendritic arbors of pyramidal cells often have two distinct conical arbors, one at the apex and the other at the base of the pyramid-shaped cell body. This configuration corresponds to a *biconical radiation* and may be characterized by different afferents contacting the basal versus apical domains. Furthermore, the length of an apical dendrite of a cortical pyramidal cell depends on how far the cell body is from the outermost layer in which it ramifies its apical tuft. Cells very near the outermost layer usually do not have an apical stem at all, since one is not required to reach appropriate axons (Rámon Y Cajal, 1995). Other pyramidal cells may have three distinct spatial domains including the apical and basal cones, as well as a central cylinder. This pattern occurs, for example, in the large pyramidal cells of hippocampal area CA1 (Fig. 1.2a). There the apical tuft arborizes in stratum lacunosum-moleculare to receive perforant path input from entorhinal cortex. The middle cylindrical arbor in *stratum radiatum* receives the Schaffer collaterals from CA3 pyramidal cells. The basal cone extends into *stratum oriens* where it receives afferents from a more proximal part of CA3 (Amaral and Witter, 1989). A similar pattern is frequently seen among other neocortical pyramidal cells (Feldman and Peters, 1978; Prieto and Winer, 1999).

The *fan radiation* is basically an elaboration of the conical radiation that is more space-filling and is flatter. This pattern is best characterized by the cerebellar Purkinje cell dendritic arbor that synapses with a large fraction of the parallel fiber axons that pass through it (Palay and Chan-Palay, 1974; Harvey and Napper, 1991).

This summary of common arborization patterns is far from exhaustive. Many other arbors can be characterized by elaborations on or combinations of the basic patterns outlined in Table 1.2. Mitral cells of the olfactory bulb, for example, can exhibit a number of variations such as a laminar radiation of secondary dendrites from the soma or a branch in the apical stem giving rise to two separate dendritic tufts (Kishi et al., 1982). The apical stem of pyramidal cells in CA1 may likewise bifurcate midway through stratum radiatum, giving rise to a pair of conical tufts (Bannister and Larkman, 1995a). Some types of neocortical pyramidal cells have an essentially stellate or planar arbor around the cell body, rather than a conical arbor of basal dendrites (Ramon Y Cajal, 1995; Prieto and Winer, 1999).

Several approaches have been developed to estimate the density of dendritic arborizations (Uylings and van, 2002; Scorcioni et al., 2004). The simplest scheme is to count the number of branch points in the entire dendritic arbor (Table 1.1). The *centrifugal method* identifies dendrites by their branching order, with primary dendrites emerging from the cell soma, their first branches as secondary with increasing order

until the tips are reached; the number of dendrite segments of each order characterizes arbor branching (Fig. 1.4). The Sholl analysis is the most widely used centrifugal analysis method (Sholl, 1953; Sholl, 1967), and modern, computer-assisted analyses are available that are well-documented and referenced (http://fiji.sc/Sholl_Analysis). Such schemes show how branched a neuron is but do not measure the degree to which the branches fill the space of the dendritic arbor.

The *fractal dimension* is an estimate of the degree to which an arborization fills its spatial domain. From basic geometry, linear objects have a dimension of 1; planar objects have a dimension of 2; solid objects, such as a sphere, have a dimension of 3; and *fractal* objects fill a fraction of the space in which they are embedded. Dendritic arbors are not fractal objects in the strict mathematical sense, but the concept of a fractional dimension is useful for quantifying their space-filling properties (Smith, Jr. et al., 1989; Kniffki et al., 1994; Panico and Sterling, 1995; Fernández and Jelinek, 2001). Selective arborizations have fractal dimensions close to 1 whereas sampling arborizations have fractal dimensions greater than 1 but less than the dimension of the spatial domain in which they arborize. Space-filling arborizations have fractal dimensions closer to the dimension of the geometrical domain they occupy, namely close to 2 for planar domains and closer to 3 for solid domains such as spheres. As with the Sholl analysis, there are modern, computer-assisted approaches available to perform fractal analyses of dendritic arbors that are well-documented and referenced (http://rsb.info.nih.gov/ij/plugins/fraclac/fraclac.html).

Some examples illustrate the effect of the branching pattern and fractal dimension on connectivity. Pyramidal neurons have selective arborizations in a three-dimensional volume with fractal dimensions of about 1.4-1.5 relative to a 3.0 that would fill the volume they occupy (Porter et al., 1991; Scorcioni et al., 2004). In contrast, retinal ganglion cells have essentially two-dimensional arbors, with a fractal dimension of about 1.5 (Wingate et al., 1992; Fernández and Jelinek, 2001). The fractal dimension of the Purkinje cell dendritic arbors ranges from a value of 1.13 in lamprey up to a value of 1.86 in humans, showing an increase with phylogeny to a nearly complete coverage of the 2D area they occupy (Takeda et al., 1992). To understand how the differences in fractal dimension relate to differences in connectivity, consider the retinal ganglion cell which has a *sampling* planar arbor covering 25,000 μm^2 and has a fractal dimension of 1.5 but receives only 2000 synapses (Sterling, 1990). In contrast, a Purkinje cell with a *space-filling* planar arbor covering and area of 50,000 μm^2 with a fractal dimension above 1.5 receives about 160,000 synapses (Smith, Jr. et al., 1989; Harvey and Napper, 1991). Somewhere in between, the dendritic arbors of hippocampal CA1 pyramidal cells receive about 20,000-30,000 synapses (Shepherd and Harris, 1998).

These analyses suggest that the complexity of the dendritic arbor reflects a propensity for connectivity; however, the actual connectivity also depends upon the axonal arborization pattern and the direction of axonal projections relative to the dendritic arbor. For example, parallel fiber axons are orthogonal to the dendritic tree of the Purkinje cell, permitting only a few synapses per axon per dendritic arbor (Palay and Chan-Palay, 1974; Harris and Stevens, 1988a; Xu-Friedman et al., 2001). In contrast, the climbing fiber from the inferior olive arborizes within the plane of a single Purkinje cell dendritic arbor, wrapping itself around the dendrite and forming many

synapses (Harvey and Napper, 1991; Xu-Friedman et al., 2001). Similarly, pyramidal cells may receive many synapses from a single axon which runs parallel to a dendritic segment or a few synapses from axons which traverse its dendrites perpendicularly (Sorra and Harris, 1993). Thus, dendritic arbors provide a rich array of patterns that provide capacity for both specificity and diversity in connectivity. The pattern of the dendritic arbor is also sensitive to experience (Volkmar and Greenough, 1972; Greenough et al., 1973; Chang and Greenough, 1982). How particular arbor morphologies affect physiology, behavior, and capacity for learning is examined in other chapters.

Intracellular structure of dendrites

Dendrites contain numerous subcellular structures that provide local resources at a distance from the soma. These structures include the Golgi apparatus, rough endoplasmic reticulum with ribosomes, free polyribosomes, smooth endoplasmic reticulum, mitochondria, cytoskeletal elements, smooth vesicles, and organelles of the endosomal pathways. These structures provide dendrites with the resources needed to respond rapidly to local changes in synaptic efficacy.

Electron microscopy reveals that the contents of large proximal dendrites are similar to those in the cell soma (Fig. 1.5a). The *Golgi apparatus* (Fig. 1.5a) and the *rough endoplasmic reticulum* (Fig. 1.5b) extend well into the proximal dendrites. These also form mobile units called Golgi outposts that occur especially at dendritic branch points but can move into the thinner more distal dendrites as well (Horton and Ehlers, 2003; Horton and Ehlers, 2004; Horton et al., 2005; Cui-Wang et al., 2012). The Golgi apparatus is involved in posttranslational modifications of proteins that are synthesized by ribosomes on the rough endoplasmic reticulum. As discussed later, the spine apparatus has structural and molecular composition suggesting that it too may be a Golgi outpost that occurs in some dendritic spines (Spacek, 1985a; Harris and Spacek, 1995; Pierce et al., 2000; Pierce et al., 2001).

Polyribosomes are clusters of free ribosomes that occur throughout the cytoplasm of dendrites (Fig. 1.5b) and in some dendritic spines and other dendritic synaptic specializations as discussed in later sections. Whereas the rough endoplasmic reticulum synthesizes transmembrane proteins, polyribosomes synthesize cytoplasmic proteins. Thus, proteins can be synthesized locally in the dendrite; although the ribosomes themselves are synthesized in the nucleolus and ribonucleic acids (RNAs) are transcribed in the nucleus, and both are subsequently transported into the dendrites (Bassell et al., 1998; Krichevsky and Kosik, 2001).

Smooth endoplasmic reticulum (SER) is the largest subcellular organelle, forming an essentially continuous network throughout neurons (Harris and Stevens, 1988a; Harris and Stevens, 1989; Martone et al., 1993; Spacek and Harris, 1997; Cooney et al., 2002). Hypolemmal cisternae (Fig. 1.5c) form junctions between SER and the plasma membrane (Henkart et al., 1976) where store-operated calcium channels regulate the replenishment of calcium in SER from the extracellular space among other functions (Majewski and Kuznicki, 2015). In single sections, the SER usually appears as tubules

or flattened cisternae with a clear interior that is bounded by a wavy membrane (Fig. 1.6). In the three-dimensional view obtained by reconstruction from serial sections the continuous reticulum becomes apparent throughout dendrites and some spines (Fig. 1.7). SER regulates calcium locally and provides posttranslational modification and trafficking of integral membrane proteins (Higley and Sabatini, 2008; Ehlers, 2013). In the dendritic shaft, SER forms local areas of complexity that retain and enhance delivery of cargo to nearby synapses (Cui-Wang et al., 2012).

Mitochondria in dendrites are typically rod-shaped organelles running parallel to the long axis of the dendrite, or curving into a dendritic branch (Fig. 1.5). They vary greatly in length, with single mitochondria extending more than 10 μm, while others can form a branched network more than 25 μm long (Popov et al., 2003; Popov et al., 2005). In thin dendrites (<0.5 μm diameter), a single mitochondrion usually lies in the center of the SER network (Fig. 1.7), and the SER is often found to surround individual mitochondria (Fig. 1.9 (Spacek and Lieberman, 1980)), similar to how SER surrounds the nucleus. This intimate relationship between SER, mitochondrial, and nuclear membranes suggests inter-organelle communication, perhaps to regulate calcium during RNA synthesis, which occurs both in mitochondria and in the nucleus. In stratum radiatum of area CA1, mitochondria comprise about 2% of the intracellular volume in the apical stem dendrites, while filling 13% of the thinnest dendritic branches of the apical tuft (Nafstad and Blackstad, 1966). Mitochondria accumulate in dendrites at large synaptic specializations, for example, in thalamic nuclei (Lieberman and Spacek, 1997) and in highly branched synaptic specializations of the CA3 pyramidal neurons known as thorny excrescences (Chicurel and Harris, 1989; Rollenhagen et al., 2007). As is known from timelapse movies in cell culture (Overly et al., 1996), mitochondria are highly dynamic structures and can be redistributed in response to metabolic demands to regions of synaptogenesis or enlarging synapses (Li et al., 2004; Kraev et al., 2009).

The *cytoskeleton* of dendrites is composed of *microtubules*, *neurofilaments (intermediate filaments)*, and *actin filaments (microfilaments)*. Microtubules are long, thin structures, ~25 nm in diameter and ~90 μm long (Fiala et al., 2003), that are usually oriented parallel to the longitudinal axis of the dendrite, although they can be found to curve into dendritic branches from the parent dendrite. In regions of the dendrite that are relatively free of organelles, the microtubules are packed in a regular array at a density of 50-150 per μm^2, typically spaced at 80-200 nm (Fig. 1.6a). The number of microtubules in a dendritic cross-section is proportional to the dendrite caliber (Fiala et al., 2003) that is also proportional to the number of spines per micron length of dendrite (Harris et al., 2007; Bourne and Harris, 2011a). Microtubules are the "railroad tracks" of the cell, and they play an important role in the transport of mitochondria and other organelles (Overly et al., 1996; Ehlers, 2013). Microtubules transport SER which leads to local elaboration and redistribution of dendritic SER (Cui-Wang et al., 2012). In regions of a dendrite with a lot of SER, the microtubules are more widely dispersed (Figure 1.6b). CLIMP63 is an integral membrane protein in SER that is phosphorylated by protein kinase C (PKC), which causes SER to dissociate from microtubules and become more elaborate (Klopfenstein et al., 1998; Vedrenne et al., 2005; Cui-Wang et al., 2012). In contrast, where CLIMP63 is dephosphorylated SER is associated with microtubules and becomes straighter and more tubular (Cui-Wang et

al., 2012). As indicated above, when SER is more elaborate, cargo is slowed and can be offloaded to support synapses and other structures in the neighborhood; whereas simplification of SER enhances movement of proteins and other cargo and slows offload. Three-dimensional reconstructions reveal that the SER is a rather continuous network that often surrounds the mitochondrion in thin dendritic branches (Fig. 1.7).

Neurofilaments (10 nm in diameter) occur in dendrites but are more common in axons, where they are important for radial growth (Yuan et al., 2012). *Actin filaments* (7 nm in diameter) constitute the bulk of the cytoskeleton between microtubules, and as discussed below, the actin filaments tend to be more highly concentrated in dendritic synaptic specializations, especially filopodia and dendritic spine necks, where they provide a means for rapid changes in shape.

Organelles of the endosomal pathway are involved in membrane protein sorting and recycling and are commonly found in dendrites (Cooney et al., 2002; Park et al., 2006). *Coated pits* and *coated vesicles* represent the initial step in endocytosis and are frequently seen at the plasma membrane of dendrites (Fig. 1.8a). The cytoplasmic coat is composed of *clathrin*, giving it a distinctive periodic structure (Fig. 1.8c). Coated vesicles and coated pits occur more frequently in dendrites during development (Altman, 1971) and during periods of synaptic remodeling (McWilliams and Lynch, 1981). *Recycling endosomes* appear as tubular compartments that can be distinguished from SER by their darker interior, more uniform diameter, smooth (as opposed to wavy) membrane, and the frequent occurrence of specialized coats at the ends of the tubule. These coated ends represent sites of budding of recycling vesicles that are bound for the cell membrane. Thus, single *smooth vesicles* are generated when these vesicles lose their coats and are then recycled back to the plasma membrane. In addition, smooth vesicles of varying dimensions can be transported from the soma or other parts of the cell along microtubules. *Sorting endosomes* can be identified by the occurrence of similar tubular compartments connected to larger, spherical organelles with interior vesicles. These spherical compartments mature into *multivesicular bodies* that separate from the sorting endosome, and eventually become late endosomes and lysosomes (See Figs. 1.5b,d above). Thus, multivesicular bodies in dendrites occur alone or in conjunction with the sorting endosome compartments (Fig. 1.8b, d).

Autophagy is a normal process that occurs in dendrites as evidenced by the presence of *macroautophagosomes,* a*utophagosomes and autophagosomal complexes* (Nixon, 2007; Nixon, 2013; Wolfe et al., 2013; McBrayer and Nixon, 2013). Depending on the stage in the degradation process, these structures are characterized by an SER-like structure that forms a double-walled delimiting membrane and surrounds other organelles (e.g. Fig. 1.12, vac), and ultimately sends them to the lysosome.

Dendrites contain other membranous subcellular structures. Amorphous vesicular clumps of membrane are common in dendritic growth cones and at sites of new synaptogenesis along dendrites and in dendritic growth cones (Fiala et al., 1998). They also appear to be critical for the growth and formation of dendritic spines during development and synaptic plasticity (Park et al., 2006).

Structure of synaptic specializations of dendrites

The potential for connectivity is established primarily by the patterns of dendritic and axonal arborization, and secondarily by the formation of a variety of synaptic specializations emerging from the dendrites (Table 1.3).

Shaft synapses reside directly on the surface of the dendrite without obvious changes in the dendritic dimensions at the synapses (e.g. Fig. 1.9). Both excitatory and inhibitory axons can form synapses directly on the dendritic shafts throughout the dendritic arbor. In hippocampus and elsewhere the interneuron dendrites have most of their synapses directly on the dendritic shafts (~95%) with only a small fraction on dendritic specializations or protrusions (~5%) (Harris et al., 1985; Harris and Landis, 1986; Ascoli et al., 2008). In contrast, 95% of synapses onto the dendrites of CA1 pyramidal cells are located on dendritic spines, while shaft synapses make up only 5% (Harris et al. 1992; Kirov et al. 1999).

Varicosities in the dendrite are one type of synaptic specialization that can be found in certain neurons, such as amacrine cells of the retina, where dendritic varicosities both receive synapses from rod bipolar cells and make reciprocal synapses back onto the bipolar cells (Ellias and Stevens, 1980). Under normal, non-pathological conditions, many of the cortical, hippocampal, and cerebellar nonspiny interneurons also have dendritic varicosities containing subcellular components that support axo-dendritic synapses (Harris and Landis, 1986; DiFiglia and Carey, 1986; Ascoli et al., 2008).

Filopodia are transient synaptic specializations of dendrites. All neurons exhibit dendritic filopodia during development when extracellular space separates potential synaptic partners (Morest, 1969). Filopodia are identified in 3DEM by their length (often extending more than 2 microns) and a somewhat denser cytoplasm than mature spines; when visualized in culture, they are highly dynamic, extending and retracting within a few minutes (Dailey and Smith, 1996; Fischer et al., 1998), which could explain the diversity of lengths captured in 3DEM (Fiala et al., 1998). After the developmental period filopodia diminish (Dunaevsky et al., 1999; Grutzendler et al., 2002) and then are usually distinguished from dendritic spines only by the absence of synapses (Bourne and Harris, 2011a). Even during synaptogenesis, most filopodia bear no synapses, but some filopodia make small synaptic contacts along their lengths with multiple presynaptic axons (Fiala et al., 1998). Multiple synapses with different axons can also be found surrounding the base of filopodia (Fiala et al., 1998), consistent with the rapid migration of synaptic proteins along filopodia in culture (Marrs et al., 2001). Long filopodia (>1 micron) are rarely seen on dendrites in normal brain beyond two weeks postnatal, possibly because the more mature neuropil is densely packed with axonal boutons; hence, even a short dendritic outgrowth would encounter multiple potential synaptic partners. During maturation filopodia are generally replaced with shaft synapses, stubby spines, or other types of synaptic specializations (Harris, 1999).

Simple dendritic spines are the most common synaptic specializations of dendrites (Fig. 1.10), being the site of more than 90% of excitatory synapses across brain regions. *Simple spines* have a *sessile* shape with no distinction between the neck and head diameters, or a *pedunculated* shape that has been described as thin or mushroom shaped (Fig. 1.10e). In the mature brain, 3DEM has revealed that simple spines vary greatly in

size, with volumes ranging from less than 0.01 μm^3 to more than 1.5 μm^3 (Table 1.4). Simple spines of different sizes and shapes can be neighbors on the same parent dendrite (Harris and Stevens, 1988b; Harris and Stevens, 1989) and occasionally form synapses with the same presynaptic bouton (Sorra and Harris, 1993; Sorra et al., 1998; Fiala et al., 2002a). The separation of simple spines into thin-necked and thick-necked varieties may be functionally relevant since the presence of a neck constriction can serve to isolate the spine head compartment from the dendrite (Holmes 1990; Koch and Zador 1993; Svoboda *et al.* 1996) and influence charge transfer and network properties (Yuste, 2013).

Additional types of simple spines are often found on specific neurons. One example is the bent sessile spines in cerebellar dentate nucleus called *crook thorns* (Chan-Palay 1977). The granule cells of the olfactory bulb have particularly large pedunculated spines sometimes referred to as *gemmules*. These spines may be 5 μm long, with heads 1-2 μm in diameter (Cameron *et al.* 1991).

Branched spines are two or more simple spines that share a common stalk (Table 1.3). The individual branches exhibit the same range of morphologies as simple spines, and each branch synapses with a bouton from different axons in mature brain (Harris and Stevens, 1988a; Harris and Stevens, 1989; Trommald and Hulleberg, 1997; Sorra et al., 1998). Apparently, branched spines are formed by accidental proximity of spine origins. Branching is a rare event because spine origins exhibit a non-random tendency to separate (Trommald et al., 1995; Ward et al., 1995), thus only ~2% of all dendritic protrusions on CA1 pyramidal cells (Harris et al., 1992) or dentate granule cells (Trommald and Hulleberg, 1997) are branched. Branched spines are more frequent on dendrites with higher spine densities such as Purkinje cell dendrites where approximately 6% of spines are branched (Harris and Stevens, 1988a). In addition, higher spine densities lead to larger numbers of branches per branched spine. Up to 5 branches have been found on Purkinje cell branched spines (Harris and Stevens, 1988a), while CA1 pyramidal cell branched spines rarely have more than 2 branches (Sorra *et al.* 1998).

Synaptic crests are specializations found occasionally on spiny neurons throughout the brain, but especially concentrated on the dendrites of the habenula, subfornical organ, and interpeduncular nucleus (Milhaud and Pappas, 1966; Akert et al., 1967; Lenn, 1976). Crest synapses are formed by two axons on either side of the thin lamellar neck of the crest. The synapses are closely apposed inside the crest and may exhibit characteristic subjunctional bodies connecting the two postsynaptic densities. In some instances a synaptic crest can contain multiple folds with many pairs of crest synapses (Lenn, 1976).

Synaptic complexes called glomeruli often occur when large axon terminals interact with particular dendrites. The dendrites extend multilobed protrusions into the glomeruli and make many synaptic contacts. A simple example is the *claw endings* of the dendrites of cerebellar granule cells (Fig. 1.1), which make several synapses with a single mossy cell axon terminal (Eccles et al., 1967). These cerebellar glomeruli also host *brush endings* of the unipolar brush cells, multilobed protrusions that are both presynaptic to the claw endings of the granule cells and postsynaptic to mossy fibers, which may

account for their unusual appearance (Floris et al., 1994; Mugnaini et al., 1994; Mugnaini and Floris, 1994).

Thorny excrescences are another type of synaptic specialization associated with large axonal boutons. These specializations are exemplified by those found in the thalamus where, in a reconstructed glomerulus of the ventrobasal thalamic nucleus, 44 synapses were located on a single excrescence that invaginated a giant lemniscal bouton (Spacek and Lieberman, 1974). Mossy fiber axons from dentate granule cells synapsing onto CA3 pyramidal cells are another classic example (Chicurel and Harris, 1992; Hama et al., 1994). The complexity of the CA3 thorny excrescences varies, with some having as many as 16 lobes and others having just a few. Usually, all of these lobes synapse with the same presynaptic bouton, but in some cases one or more lobes synapse with different axons.

Racemose appendages have a more sparsely lobed appearance and are common on neurons in inferior olive (Ruigrok et al., 1990) and lateral reticular nucleus (Hrycyshyn and Flumerfelt, 1981a; Hrycyshyn and Flumerfelt, 1981b; Hrycyshyn and Flumerfelt, 1981c). This type of protrusion can also be found on spiny neurons such as neocortical pyramidal cells.

Coralline excrescences are found on dendrites of the small neurons of the cerebellar and vestibular nuclei. These complex dendritic varicosities exhibit numerous synaptic protrusions (Chan-Palay, 1977), and sometimes they also have thin tendrils similar in appearance to filopodia (Morest, 1969; Sotelo and Angaut, 1973; Angaut and Sotelo, 1973), leading to the suggestion that the coralline excrescences are growth processes on adult dendrites.

The dendritic synaptic specializations outlined in Table 1.3 do not describe all of the shapes of synaptic specializations of dendrites. Furthermore, individual dendritic segments exhibit a wide variety of spine types as well as other synaptic specializations. Thus, the shape of dendritic synaptic specializations is not fixed by the postsynaptic neuron, but appears to reflect the source and activation history of the presynaptic partner. Furthermore, synaptic specializations can be highly dynamic structures, capable of structural change throughout life. This structural synaptic plasticity blurs morphological classifications, and many related and intermediate forms are to be expected. For example, filopodia become dendritic spines, and small spines have been shown to grow or shrink over time and with experience, as discussed further below. In addition, since the distribution of spine dimensions is broad and essentially continuous and modern super-resolution microscopy and 3DEM provide a means to obtain reasonably accurate measurements, we advocate moving to a system where actual measurements replace classification of shapes in the future. Furthermore, as discussed next, the subcellular composition of spines and other specializations further by their capacity to undergo calcium-mediated or protein-synthesis dependent changes in structure and molecular composition.

Composition of synaptic specializations of dendritic

The diversity of shapes of synaptic specializations is accompanied by diversity in their intracellular composition. Like the dendritic shaft, different dendritic synaptic

specializations contain different intracellular components, including various synaptic and adhesive junctions, smooth endoplasmic reticulum, the spine apparatus (possible Golgi outpost), rough endoplasmic reticulum and polyribosomes, mitochondria, microtubules, smooth vesicles, and organelles of the endosomal and recycling pathway. The presence or absence of perisynaptic astroglial processes influences the structure and composition of the dendritic synaptic specializations. Furthermore, the size of a synaptic specialization correlates with the composition of subcellular structures. Thus, even within and surrounding the synaptic specializations, resources are present that can respond rapidly to local changes in synaptic efficacy.

Postsynaptic densities: The synaptic specializations of dendrites receive chemical synapses consisting of apposed membranes separated by a gap called the synaptic cleft (Fig. 1.11, 1.12). Neurotransmitters released from synaptic vesicles on the presynaptic side of the cleft diffuse across the cleft to activate receptors in the postsynaptic membrane. The presynaptic element is usually a varicosity or end bulb of an axon, called a bouton. In aldehyde-fixed tissue, several different types of chemical synapses can be distinguished based on the size and shape of the presynaptic vesicles and perisynaptic structures (Colonnier, 1968; Peters and Palay, 1996). Two principal types are commonly referred to as asymmetric and symmetric synapses. Asymmetric synapses are characterized by round presynaptic vesicles ~30-50 nm in diameter and a prominent postsynaptic density (Fig. 1.11a, b; Fig. 1.12a, b). The postsynaptic density is a densely stained structure that contains numerous receptors, structural proteins, and signaling molecules that are important for synaptic transmission and plasticity (Kennedy, 2000). The synaptic cleft also contains dense-staining material (Fig. 1.11b), which likely contains the extracellular components of receptors and other signaling or adhesion molecules. Symmetric synapses have a much thinner postsynaptic density, matched by a nearly equal density on the presynaptic side, where many of the presynaptic vesicles appear flattened (Fig. 1.11c, 12a). Asymmetric synapses are usually excitatory and use the neurotransmitter glutamate, whereas symmetric synapses use the inhibitory neurotransmitters GABA or glycine and their molecular composition of receptors and downstream signaling molecules matches these structural and functional distinctions (Harris and Weinberg, 2012).

Asymmetric and symmetric synapses are differentially distributed along dendrites. By definition, simple spines have an excitatory asymmetric synapse located on the spine head. Occasionally, simple spines have more than one synapse (Spacek and Hartmann, 1983; Fiala et al., 1998; Bourne and Harris, 2011a). The second synapse can be either symmetric or asymmetric (Jones and Powell, 1969). For example, in visual cortex 84% of synapses are asymmetric, while 16% are symmetric (Beaulieu and Colonnier, 1985). Most of these asymmetric synapses (79%) occur on simple dendritic spines, while 21% occur on dendrite shafts, and very few (0.1%) are found on cell bodies. The symmetric synapses are much less frequent and yet their positioning might effectively nullify the excitatory input because most occur directly on the dendrite shafts (62%), 31% occur on a fraction of the dendritic spines, and 7% occur on cell bodies and axon initial segments. Symmetric synapses are only 7% of all dendritic spine synapses but 93% of all soma synapses in visual cortex. In neostriatum, for

another example, approximately 8% of spines receive both an excitatory asymmetric and an inhibitory symmetric synapse (Wilson et al., 1983). Some striatal neurons make reciprocal connections with substantia nigra, and in this field 39% of their spines are contacted by a different type of symmetric synapse containing large, pleomorphic vesicles which are probably dopaminergic (Freund et al., 1984). Glomeruli often contain both excitatory and inhibitory axon terminals. Thus, it is common for dendritic synaptic specializations that project into glomeruli to receive multiple types of synaptic contacts. For example, the racemose appendages of inferior olivary neurons receive both excitatory and inhibitory synapses (De Zeeuw et al., 1990).

Cell adhesion junctions (puncta adhaerentia) and nascent zones adjacent to synapses: Cell-adhesion junctions, sometimes referred to as puncta adhaerentia (Fig. 1.12a, 1.13), are characterized by pre- and postsynaptic thickenings but no presynaptic vesicles. They can be located at the edges of the postsynaptic densities of dendritic spines and other synaptic specializations (Uchida et al., 1996; Spacek and Harris, 1998; Benson and Huntley, 2010). Extensive adherent contacts form a meshwork in glomeruli of thalamic relay nuclei (Lieberman and Spacek, 1997). Cell adhesion junctions contain a host of adhesion molecules (e.g. cadherins, neuroligins, and neurexins) with associated signaling cascades that differentiate them from the receptor-containing portions of the postsynaptic density (Fields and Itoh, 1996; Fannon and Colman, 1996; Benson and Huntley, 2010).

In addition to the puncta adhaerentia, we have identified the *nascent zone* (Fig. 1.13), an ultrastructurally distinct region at the edge of synapses in the intact mature hippocampus (Bell et al., 2014), which was previously described as a vesicle-free transition zone (Spacek and Harris, 1998). Both nascent zones and active zones have a postsynaptic density, but, unlike the active zone, the presynaptic side of a nascent zone lacks the small clear synaptic vesicles that are required for glutamate release. Unlike puncta adhaerentia, nascent zones have no presynaptic thickening. Synaptic edges are highly dynamic regions where AMPA-type glutamate receptors (AMPARs), which mediate fast excitatory transmission, diffuse laterally until they are stabilized by activity (Choquet and Triller, 2013; MacGillavry et al., 2013). However, even if AMPARs were present in a nascent zone, the absence of presynaptic vesicles could render the nascent zone functionally silent because the diffusion path from release sites is too far (Franks et al., 2002; Franks et al., 2003; Raghavachari and Lisman, 2004; Christie and Jahr, 2006; MacGillavry et al., 2013; Nair et al., 2013). Their distinct locations, composition, and morphology likely serve to modulate synaptic efficacy since their disassembly and reassembly may be needed for synaptic plasticity (Luthl et al., 1994; Muller et al., 1996; Tang et al., 1998) and recent 3DEM results show that they disappear early and indeed are reassembled at 2 hours after the induction of long-term potentiation (Bell et al., 2014).

The postsynaptic densities and associated adhesions exhibit size-dependent variations in morphology (Spacek and Hartmann, 1983; Harris and Stevens, 1988a; Harris and Stevens, 1989; Humeau et al., 2005; Nicholson and Geinisman, 2009). Most synapses have a continuous postsynaptic density when viewed in 3DEM, often called macular in shape (Fig. 1.9, 1.10e (see T spines), 1.12b, 13a). Larger postsynaptic densities often exhibit interior regions devoid of pre- and postsynaptic density which

can be U-shaped, annular, or exhibit multiple holes, and are often called perforated (Fig. 1.12a, 13b), segmented, or multifocal synapses (Geinisman et al., 1987; Sorra et al., 1998).

Both macular and perforated synapses occur on a variety of dendritic synaptic specializations. When located on spines, the synaptic area occupies approximately 10% of the surface area of the spine head (Spacek and Hartmann, 1983; Harris and Stevens, 1988a; Harris and Stevens, 1989). This relationship is consistent over different spine morphologies and neuron types (Table 1.4) and appears also to hold for more complicated synaptic specializations as well, such as the thorny excrescences of CA3 (Chicurel and Harris, 1992). Spine surface area, spine volume, bouton volume, and number of synaptic vesicles correlate with synapse size in most cases (Harris and Stevens, 1988a; Harris and Stevens, 1989; Lisman and Harris, 1993; Schikorski and Stevens, 2001). Thus, smaller thin spines have smaller synapses, which tend to be macular, and larger mushroom spines have larger synapses, which can be perforated (Sorra et al., 1998; Bourne and Harris, 2007). Larger synapses contain more receptors and other signaling molecules, and therefore represent more efficacious connections (Nusser, 2000; Matsuzaki et al., 2001; Tanaka et al., 2005; Holderith et al., 2012). Differences in synaptic efficacy have important implications for both long-term information storage and short-term neurotransmission. For example, excitatory synapses in the most distal apical dendrites of CA1 pyramidal cells are more often larger, perforated synapses than those synapses more proximal to the cell body (Megias et al., 2001; Nicholson et al., 2006). This property may help compensate for distance-dependent attenuation of postsynaptic potentials (see Chapter 8).

It has been suggested that synapse perforations may be related to synaptic plasticity and represent an intermediate stage in a process of synapse proliferation through splitting (Jones and Harris, 1995; Luscher et al., 2000). However, dendritic spines do not split (Sorra et al., 1998; Fiala et al., 2002a). Instead, perforations in the PSD appear to be a postsynaptic counterpoint to presynaptic vesicle membrane fusion, prior to bulk endocytosis, which then incorporates a postsynaptic spinule to knit the PSD back together later (Applegate et al., 1987; Applegate and Landfield, 1988; Geinisman et al., 1996; Spacek and Harris, 2004; Bourne and Harris, 2011a; Bourne and Harris, 2012).

Smooth endoplasmic reticulum (SER): Some synaptic specializations also contain elements of the dendritic SER network (Figs. 1.12 and 1.14). In pyramidal neurons of the cerebral cortex and hippocampus, only about 15% of dendritic spines contain SER, and this organelle is mostly absent from thin spines (Spacek and Harris, 1997). All dendritic spines of cerebellar Purkinje cells contain SER (Spacek, 1985a; Harris and Stevens, 1988a). In claw endings of cerebellar granule cells, each mitochondrion is surrounded by a single cistern of SER. Organelles derived from SER also appear subjacent to the puncta adhaerentia on both pre- and postsynaptic sides.

The spine apparatus (possible Golgi outpost), rough endoplasmic reticulum and ribosomes: Large spines often possess a large, perforated synapse and contain a spine apparatus (Fig. 1.12a). As mentioned above, the spine apparatus has structural and molecular features similar to the Golgi apparatus (Gray, 1959; Spacek and Harris, 1997; Pierce et al., 2000; Pierce et al., 2001; Deller et al., 2007). The largest mushroom spines

and gemmules often contain the spine apparatus, as do the thorny excrescences of hippocampal area CA3. The spine apparatus can also be found in association with polyribosomes (Fig. 1.14b). High concentrations of polyribosomes have been found in the lobes of thalamic thorny excrescences (Fig 1.15) and those of the CA3 pyramidal cells (Chicurel and Harris, 1989). Under quiescent conditions, only about 12% of simple dendritic spines contain *polyribosomes* (Steward et al., 1996; Ostroff et al., 2002). During tetanus-induced long-term potentiation, polyribosomes increase dramatically in spines (Ostroff et al., 2002; Bourne et al., 2007), contrasting with theta-burst induction of long-term potentiation, where polyribosome frequency increases transiently in several spines, but then concentrates by two hours in spines with the most enlarged synapses (Bourne and Harris, 2011b). The spine apparatus is often found to have a structural association with puncta adhaerentia and nascent zones, indicating a possible role in synthesizing or maintaining them (Spacek and Harris, 1998; Bell et al., 2014). In addition, this location would enhance signaling via metabotropic glutamate receptors, which are also concentrated at the edges of excitatory synapses (Baude et al., 1993; Kennedy, 2000).

Mitochondria: Small synaptic specializations such as filopodia and simple dendritic spines rarely contain mitochondria as most are too small. Larger dendritic synaptic specializations often contain mitochondria. Gemmules of olfactory bulb granule cells often have mitochondria in the head, and since these spines make reciprocal synapses on mitral cell dendrites, it has been suggested that the presence of these mitochondria may be related to their presynaptic function (Cameron et al., 1991). Other specializations with both postsynaptic and presynaptic functions, such as the varicosities of AI amacrine cells and the brush endings of unipolar brush cells, likewise contain numerous mitochondria. Although the large thorny excrescences and claw endings do not have synaptic vesicles, they may contain a mitochondrion, suggesting a role beyond vesicular release. The larger synaptic specializations of the relay neurons of lateral geniculate nucleus also contain many mitochondria but have no presynaptic function (Wilson et al., 1984). During development, mitochondria appear to visit the base of dynamic dendritic protrusions in culture (Li et al., 2004). Hence, mitochondria may provide differential support in the forms of calcium regulation, local protein synthesis, and production of ATP, depending on the function, size, and developmental status of a synaptic specialization.

Microtubules: Small dendritic protrusions such as simple spines and filopodia have cytoskeletons based primarily on actin rather than microtubules, although tubulin is ubiquitous in subcellular fractions of the postsynaptic density. Actin-based cytoskeletons are thought to facilitate rapid, calcium-induced changes in shape (Fifkova, 1985; Fischer et al., 1998; Halpain et al., 1998). Microtubules are not readily observed through serial section electron microscopy in mature hippocampal, cortical, or cerebellar dendritic spines under normal conditions, although they do occur normally in the extra-large CA3 thorny excrescences (Ebner and Colonnier, 1975; Chicurel and Harris, 1992) and in hippocampal and cortical dendritic spines during development, apparently emanating from the spine apparatus (Westrum and Gray, 1977; Westrum et al., 1980). During the short period of synaptic quiescence after making a hippocampal slice, microtubules protrude into mature dendritic spines; however, these spine

microtubules are no longer detected by 30 minutes after the slice has recovered *in vitro* (Fiala et al., 2003). Recent work in hippocampal cultures suggests that microtubules are highly dynamic, and rapidly enter and retract from dendritic spines (Hu et al., 2008; Gu et al., 2008; Jaworski et al., 2009; Dent et al., 2011) such that at any one moment less than 1% of spines may contain a microtubule. This transience, along with the sensitivity to calcium, may explain why microtubules are rarely detected in a polymerized state in mature dendritic spines of aldehyde-fixed brain *in vivo*.

Organelles of the endosomal and recycling pathways: Smooth and coated vesicles and elements of the endosomal pathway also occur in synaptic specializations. The discrete tubules and vesicles of the endosomal compartments are distinguished from the essentially continuous network of SER through 3DEM. In addition, recycling endosomes engulf gold particles conjugated with bovine serum albumin (BSA-gold) that had been delivered in the extracellular space of a hippocampal slice (Cooney et al., 2002). About 50% of normal hippocampal dendritic spines contain no membrane-bound organelles, whereas some spines contain endosomes and others contain SER. Only rarely does a single spine contain both organelles. An endosomal sorting complex occurs about once every 10 microns of dendritic length and hence serves about 10-20 hippocampal dendritic spines (Cooney et al., 2002). Interestingly, the endocytosis-related proteins clathrin, AP-2, dynamin (Racz et al., 2004; Lu et al., 2007), and an isoform of the exocytosis-related protein syntaxin (Kennedy et al., 2010) are all localized to a putative endocytic zone at the edge of postsynaptic densities. Endosomal compartments are dynamically regulated during synaptic plasticity and may provide a local source of new membrane for spine enlargement (Park et al., 2006). Some endosomal compartments in dendrites may also be involved in autophagocytosis, a process where proteins and other structures are engulfed by a membrane-bound organelle and incorporated into the lysosomal pathway for subsequent degradation (Bingol and Sheng, 2011). However, the complement of organelles in each instance is unique, suggesting local regulation of subcellular functions, possibly in response to different levels of neuronal activity. Extensive tubular bodies also appear in the dendritic cytoplasm subjacent to *puncta adhaerentia* (Spacek and Harris, 1998).

Dendritic spines occasionally have even smaller protrusions, *spinules*, that extend from them into the interior of surrounding structures such as boutons or glia (Westrum and Blackstad, 1962; Tarrant and Routtenberg, 1977; Sorra et al., 1998; Spacek and Harris, 2004; Richards et al., 2005). These spinules are surrounded by invaginations of apposed membrane often with a clathrin-like coat visible on the cytoplasmic side of the engulfing membrane at the tip of the invagination. Spinules in the hippocampus originate from all parts of the dendrite surface, often at the edges of synapses (Fig. 1.12b) or from within perforations (Fig. 1.16). The function of spinules is not known, however it may involve bulk membrane recycling or signaling by way of transendocytosis (Spacek and Harris, 2004). Similar structures are found on other types of synaptic specializations, such as on the claw endings of cerebellar granule cells (Eccles et al., 1967) and on the lobes of thorny excrescences (Chicurel and Harris, 1992).

Perisynaptic astroglia: Finally, synapses differ in the degree to which they are

surrounded by glial processes. In cerebellar cortex, nearly all spine synapses are completely ensheathed by the Bergmann astroglial processes (Fig. 1.16c,d (Spacek, 1985b). In contrast, only 58% of hippocampal synapses have even partial astroglial ensheathment (Ventura and Harris, 1998), which is comparable to cortical spine synapses (Spacek, 1985b). Thus many but certainly not all synapses have astrocytic processes at their perimeter, whereby neurotransmitter spillover between neighboring synapses could be detected and limited (Bergles and Jahr, 1997). Another important aspect of perisynaptic astroglia at excitatory synapses is energy metabolism. Perisynaptic astrocytes contain rich stores of glycogen that provide local energy replacement following synaptic activity (Magistretti et al., 1999). Perisynaptic astroglial processes provide crucial factors, both contact-mediated and secreted factors, towards the formation and maturation as well as the maintenance and elimination of synapses (Clarke and Barres, 2013). Interestingly, localization of perisynaptic astroglia is also highly susceptible in human hippocampus to pathology such as epilepsy (Witcher et al., 2010).

Diversity in Spine and Synapse Density across Dendritic Arbors

Neurons have been generally classified as *spiny*, *sparsely spiny*, and *nonspiny* (or *smooth*) according to the density of simple dendritic spines throughout the dendritic arbors (Feldman and Peters, 1978). Dendritic spines increase the number of potential synaptic partners for a neuron by extending the reach of dendrites to a larger pool of axons, while increasing brain volume only slightly (Swindale, 1981; Harris and Kater, 1994; Chklovskii et al., 2004). The ratio of actual synapses to the number of potential synapses, the so-called *filling fraction*, is estimated to be about 0.2 for cortical pyramidal cells (Stepanyants et al., 2002). Indeed, dense 3DEM reconstructions from hippocampal CA1 neuropil reveal that only 20% of axons touching a dendrite actually made a synapse with that dendrite (Mishchenko et al., 2010).

Classification of neurons by spine density is complicated by the fact that different dendrites of a given neuron may exhibit widely different spine densities. Even along the length of a single dendritic segment, spine densities can vary tenfold, and nominally nonspiny dendrites often exhibit a few spines. For example, a CA1 pyramidal cell in the rat has about 30,000 spines, with 55% of them located in the apical dendritic arbor and 40% in the basilar dendritic arbor (Megias et al., 2001). The spine density correlates with dendrite caliber, ranging from <1 spine per μm at the tapered dendritic tips, ~2-3 spines per μm on oblique dendritic branches, and ≥10 spines per μm along the thick apical dendrites of hippocampal CA1 pyramidal neurons as they pass through the middle of s. radiatum (Harris et al., 1992; Trommald et al., 1995; Bannister and Larkman, 1995b; Megias et al., 2001). High spine densities are found on other neuron types such as certain neostriatal neurons that have 7 spines per μm (Wilson et al., 1983; Graveland et al., 1985). By comparison, pyramidal cells of visual cortex are less spiny, averaging only about 1.5 spines μm^{-1} (Larkman, 1991).

The spiniest dendrites may be the spiny branchlets of the cerebellar Purkinje cell, with 3DEM revealing spine densities reaching 15 spines per μm (Harris and Stevens, 1988a). Thus, a single Purkinje neuron in the adult rat may have over 160,000 spines

(Napper and Harvey, 1988a; Napper and Harvey, 1988b). The giant pyramidal cells of Meynert in visual cortex have basilar dendrites and an apical dendrite in layer 5 that are densely covered with spines, few spines along the apical dendrite in layers 3-4, and a high density occurs again as the dendritic arbor reaches layer 2 (Chan-Palay et al., 1974). For most spiny neurons, the dendrites emerging from the soma receive inputs at shaft synapses; hence, like the soma, proximal dendrites are usually devoid of spines. Thus, differences in characteristic spine densities across the dendritic arbor may reflect differences in connectivity to various inputs.

Dendritic pathology

The characteristic dendritic arbors of neurons are created through a combination of intrinsic developmental programs and environmental influences, as discussed further in subsequent Chapters. The cellular environment continues to have an influence on dendrites throughout life, and a number of structural pathologies arise from various adverse conditions (Fiala et al., 2002b; Kuwajima et al., 2013). These pathologies must be distinguished from the normal changes in dendritic and synaptic structure that accompany development, learning, memory, and a host of experiences (Bourne and Harris, 2008; Bourne and Harris, 2012).

One strong influence on dendrite structure is excitatory synaptic input, as studied for many years by lesion-induced degeneration in Golgi impregnated brain tissue (Globus, 1975). Axonal inputs are necessary for proper dendrite development and maintenance. For instance, when granule cells are eliminated from the developing cerebellar cortex, Purkinje cells exhibit profoundly reduced, deformed, and miss-oriented dendritic arbors (Altman and Bayer, 1997). Dendrite structure continues to be dependent on the preservation of axonal afferents throughout adulthood, since deafferentation is followed by atrophy of the dendritic arbor (e.g. (Anderson and Flumerfelt, 1986a; Anderson and Flumerfelt, 1986b)). Consider another example from the hippocampus in which lesion of entorhinal cortex atrophies the dendritic arbors of granule cells in the dentate gyrus (Caceres and Steward, 1983). Total dendritic length is reduced to less than 2000 μm (cf. Table 1) ten days after the lesion. Most of this reduction occurs in the distal dendrites that normally receive the entorhinal input. Remarkably, the dendritic arbors of deafferented neurons often recover (at least partially) within a few months through reafferentation from sprouting axon collaterals.

Reductions in dendritic arborization are seen in many pathological conditions, such as mental retardation (Kaufmann and Moser, 2000), prionosis (Beck et al., 1975), and Alzheimer's disease (Scheibel, 1982), possibly due to neuron loss and the associated deafferentation. Even aging seems to produce a degree of dendritic atrophy (Scheibel et al., 1975; Jacobs et al., 1993; Chen and Hillman, 1999; Peters, 2002). Trophic support for the dendritic arbor may come not only from synaptic inputs but also from the synaptic connections of a neuron's axon. In the peripheral nervous system, the dendritic arbor shrinks when a neuron's axon is transected (Purves et al., 1988). In the central nervous system, however, axotomy often produces a retrograde degeneration in which the axotomized neuron dies (Ramón y Cajal, 1991). The neurodegeneration is often

characterized by an accumulation in the soma and proximal dendrites of granular endoplasmic reticulum that disintegrates and leads to chromatolysis. The signs of cell death are reflected in the dendrites as shrinking and densification of the cytoplasm, a form of dendritic pathology frequently seen after traumatic injury.

The pathological effects of deafferentation or axotomy may require days to materialize. More immediate alternations in dendrites are apparent with hypoxia or ischemia, as during stroke. Hypoxia causes a loss of energy that retards the ability of dendrites to maintain ionic polarity at the cell membrane. Abnormal dendritic varicosities are seen in brain tissue damaged by tumor (Fig. 1.17, (Spacek, 1987), convulsions (Scheibel and Scheibel, 1977), and cold temperatures. Dendritic swelling affects the cytoplasmic organelles as well. The SER can become dilated or even swollen into large vacuoles. In Purkinje cells the dendritic SER first forms into lamellar arrays of cisternae (Banno and Kohno, 1996). Mitochondria can also be swollen in dendrites following hypoxia, and microtubules can be completely depolymerized.

A number of progressive neurodegenerative disorders are associated with other forms of dendrite pathology (Hirano, 1981). A different type of dendritic varicosity containing abnormal protein aggregations known as Lewy bodies occurs in Parkinson's disease. In Creuzfeldt-Jakob disease, a form of prionosis, vacuolar dystrophy within dendrites causes a spongiform appearance of the neuropil. Other inclusions of various metabolites may fill the dendritic cytoplasm in different enzymopathies.

Pathology of synaptic specializations of dendrites

The synaptic specializations of dendrites are also prone to structural distortions by a variety of insults and diseases. The pathologies of dendritic spines have been particularly well-studied as summarized in Fig. 1.18, and reviewed in (Fiala et al., 2002b; Kuwajima et al., 2013). Two general categories of spine pathology are distinguished as pathologies of distribution and pathologies of ultrastructure.

Many conditions lead to changes in the number of dendritic spines along spiny dendrites. Spine loss commonly occurs within a few days of deafferentation. Permanent spine loss is evident in most forms of mental retardation, including those resulting from prenatal infection, malnutrition, and toxin or alcohol exposure. Spine loss is also seen in epilepsy, prionosis and various neurodegenerative disorders. Increased spine density is seen paradoxically in some types of deafferentation, such as when Purkinje cells are deprived of their climbing fiber input. Increased spine numbers have also been reported following chronic use of stimulatory drugs. In some cases, an overabundance of dendritic spines may represent a failure of normal developmental synapse elimination, as has been suggested for fragile-X syndrome (Cruz-Martin et al., 2010; Portera-Cailliau, 2012).

Absence of normal levels of presynaptic activity without the destruction of the input axons can result in a reduction in synapse and spine size, as reported in visual cortex following visual deprivation from birth (Globus, 1975). In contrast, deafferentation often results in excessive enlargement of the remaining spines and synapses as an apparent compensatory mechanism for the decreased synaptic input. Deafferentation

can also lead to lengthening of dendritic spines, and a similar distortion of dendritic spine shape is seen in mental retardation and other conditions. The unusually long and tortuous spines having no head enlargement or multiple swellings along their length resemble in many respects the filopodia seen during developmental synaptogenesis. This resemblance suggests that synaptogenic mechanisms are active in the pathological conditions and long, tortuous spines are an additional compensatory response to loss of afferents (Fiala et al., 2002b).

Another response to deafferenting conditions is the formation of axonless spines. Axonless spines exhibit an intracellular structure that looks like a postsynaptic density, but this structure does not form part of a synapse with an axon. Rather, axonless spines contact glia or the dendrites of other neurons (Spacek, 1982). Although they are observed occasionally in the normal brain, occurrences of axonless spines increase in many pathological conditions, such as developmental agenesis of cerebellar granule cells (Altman and Bayer, 1997).

Alterations in spine organelles result from diverse causes. One cause may be degeneration of the postsynaptic cell, as is often the case when the dendritic cytoplasm becomes dense and dark. Another cause may be excitotoxic injury from excessive presynaptic glutamate release, which characteristically leads to thickening of the postsynaptic density, a condition often seen in ischemia. Ischemia also induces postsynaptic density-like structures that lie free in the cytoplasm of the dendrite (Tao-Cheng et al., 2001).

Changes in spine endosomes, endoplasmic reticulum, and cytoskeleton have been occasionally observed in edema, e.g. after traumatic injury. Hydropic swelling and vacuolization of the endoplasmic reticulum of dendritic spines is frequently seen in edematous tissue. In addition to swelling, the spine apparatus can become elaborated or atrophied. Loss of ionic regulation at the plasma membrane can also lead to microtubule depolymerization in the dendrite shaft, as mentioned above.

Concluding remarks

A hundred years after Ramón y Cajal, the intricacies of the relationship between structure and function in neurons are still being discovered. The pattern of dendritic arborization is clearly related to connectivity but also contributes to dendritic computation, particularly when the dendrite is endowed with active mechanisms (Chapter 14). The synaptic specializations extended by dendrites also contribute significantly to connectivity, allowing thin dendrites to interdigitate in a relatively small brain volume. Their diverse structures presumably have diverse functions related to neuronal computation and learning (Chapter 18). What the exact role changes or differences in dendritic and synaptic structure confer during normal development, learning, and memory remains an area of active investigation. Assuming form predicts function, the diversity in dendritic and synaptic structure and composition discussed here suggests many mechanisms are available to adjust the strengths of connectivity across the brain.

Acknowledgements

For kind permission to reprint figures as indicated in the captions, the authors thank the original publishers Blackwell Publishing, Oxford, and Springer-Verlag, Berlin. Earlier editions of this chapter included substantial contributions from Dr. John Fiala, and he is thanked for those contributions, some of which are retained, and some with revision in this chapter. Marcia Feinberg, Libby Perry, Robert Smith are thanked for assistance with serial section electron microscopy. This work was supported, in part, by National Institutes of Health grants R01MH095980, R01NS074644, and R01MH104319 to KMH.

Figure Legends:

Fig. 1.1: Dendrites often look like tree branches. Thus the name derives from the Greek word for tree: *dendron*. In this image of mouse cerebellar cortex silver-impregnated using the Bielschowski method, a thick primary dendrite (arrowhead) extends from the upper right of the cell body of a Purkinje neuron. The primary dendrite branches into secondary (curved arrows) and tertiary (straight arrows) dendrites within the plane of the section. Terminal dendritic branchlets are not visible with this method. **Upper Inset:** 3DEM reveals the high density of protrusions, known as dendritic spines (small arrows). Beneath the large Purkinje cell can be seen a layer of smaller granule cell bodies (white arrows). **Lower Inset:** Higher magnification of a Golgi-impregnated granule cell (white arrow) reveals that this neuron possesses just a few, short dendrites ending in claw-like formations (open arrows).

Fig. 1.2: Neurons silver-impregnated with the Golgi method. **(a)** A pyramidal neuron from hippocampal area CA1 of the rat, in which basal and apical dendrites ramify in separate conical domains. Between these two denser domains, a few dendrites extend obliquely (arrows) from the apical dendrite as it passes through stratum radiatum. (Harris *et al.* 1980) **(b)** A thalamic projection neuron exhibits many primary dendrites extending from the cell body with a spherical radiation. (rat; reprinted with permission from Spacek and Lieberman 1974) **(c)** A pyramidal neuron from the parietal area of mouse cerebral cortex has a sparsely branching apical dendrite and a few dendrites that extend almost horizontally from the base of the cell body. All three images have been scaled to match the magnification and scale bar in **(a)**.

Fig. 1.3: Differences in dendritic arbor density reflect differences in connectivity. At one extreme are selective arborizations in which each dendrite connects the cell body to a single remote target. An olfactory sensory cell illustrated this pattern. At the other extreme lie the space-filling arborizations in which the dendrites cover a region, as with the cerebellar Purkinje cell. Intermediate arbor densities are referred to as sampling arborizations, as demonstrated by a pyramidal cell from cerebral cortex. (Drawings of neurons from Ramón y Cajal, 1995.)

Fig. 1.4: Methods for quantifying dendritic arbors. **(a)** A plot of the number of branches of each order using the centrifugal method of branch ordering. **(b)** A *Sholl plot* with counts of the number of intersections the dendritic tree makes with circles of increasing radius from the center of the soma. When three-dimensional data are available, concentric spheres are used.

Fig. 1.5: **(Opposite page)** Organelles extend from soma into the apical dendrite of an adult rat CA1 pyramidal cell. a) Nucleus (N), Golgi apparatus (G), mitochondria (M, branch points indicated by an arrow). b) rough endoplasmic reticulum (rer), polyribosomes (pr), multivesicular body (mvb). c) two arrows mark the extent of a hypolemmal cisterna of the endoplasmic reticulum (H) that also has rer in close proximity. d) Lysosome (L).

Fig. 1.6: Effect of subcellular organelles on the distribution of microtubules in the cytoplasm. **(a)** An apical dendrite (D) in the middle of hippocampal CA1 s. radiatum from an adult rat has a regular array of microtubules (arrows) interspersed with a few, narrow tubules of SER (curved arrows), and no mitochondria. **(b)** A secondary dendrite (D) of an adult mouse Purkinje cell with microtubules (horizontal arrows) interspersed between many elements of SER (curved arrows) and 9 mitochondrial profiles (M). Note that the magnification of **(b)** is exactly twice that of **(a)**.

Fig. 1.7: Reconstruction of a segment of a lateral dendritic branch (12.5 μm long) from a CA1 pyramidal cell in *stratum radiatum* of adult rat hippocampus. a) Network of smooth endoplasmic reticulum. b) A mitochondrion runs down the center of the dendrite and is surrounded by the SER network.

Fig. 1.8: Endosomes in lateral dendrites in s. radiatum of area CA1, from adult rat hippocampus. **(a)** Clathrin coated pits (arrows) are the initial step in the endosomal pathway. **(b)** A multivesicular body (mvb) with its connected tubular compartments of a sorting endosome (arrows). **(c)** A tubular endosome associated with a sorting complex has a coated tip at one end (arrow). **(d)** Three-dimensional reconstruction of the sorting complex reveals a multivesicular body with many tubules. The top of the multivesicular body is removed to reveal the interior vesicles. Clathrin coated tips are identified at the ends of a few tubules (arrows).

Fig. 1.9: An interneuron dendrite from stratum radiatum of hippocampal area CA1 in a 21-day-old rat with mostly shaft synapses. **(a)** Electron micrograph illustrating a cross-sectioned view where this dendrite hosts 3 excitatory synapses (white arrows) directly on the dendritic shaft This section also illustrates that interneuron dendrites have dispersed microtubules among a similar complement of subcellular components as the spiny dendrites described above including a close association between SER and mitochondria (black arrows, M), microtubules (mt), and a sorting endosome with a multivesicular body (mvb) illustrated on this section. **(b)** Three-dimensional reconstruction from serial section electron microscopy of a 4.6 μm segment of the dendrite reveals 45 excitatory synaptic contacts (black), 91% of which are located on the dendrite shaft and 3 on protrusions (arrows).

Fig. 1.10: Dendritic spines at increasing magnifications. **(a)** Apical dendrite of a neocortical pyramidal neuron has few spines near the soma (bottom of image) and many spines distally. (Golgi; rat) **(b)** Spiny dendrites of a CA1 pyramidal cell of hippocampus. (Golgi; rat) **(c)** High magnification of a neocortical pyramidal neuron dendrite. (Golgi; mouse) **(d)** Spiny branchlet of a cerebellar Purkinje cell. (Golgi; mouse) Images c and d reprinted with permission from Spacek and Hartmann (1983). **(e)** Three-dimensional reconstruction of a segment of CA1 pyramidal cell dendrite (D) showing typical shapes of thin (T) and mushroom (M) pedunculated spines. (serial section electron microscopy; rat)

Fig. 1.11: Asymmetrical and symmetrical synapses on dendrites of spiny neurons. **(a)** An asymmetrical synapse located on a spine head (Sp) from adult rat hippocampus illustrates the characteristic thickened postsynaptic density and round presynaptic (pre) vesicles. **(b)** High magnification image of another asymmetrical synapse from mouse cerebellum shows dense material in the synaptic cleft (white arrow). **(c)** Symmetrical synapse on the shaft of a dendrite from rat hippocampus illustrates the thin and essentially equal densities in the presynaptic (pre) and postsynaptic (D) compartments and pleiomorphic presynaptic vesicles, which are smaller and more flattened than the vesicles of an asymmetric synapse (compare to those in **a**). Scale bar in **(a)** is the same for **(c).**

Fig. 1.12: Different dendritic spines contain unique subcellular composition. **(a)** On this section, each of two dendrites (D1, D2) in rat CA1 stratum radiatum give rise to large spines (curved arrows) that contain a spine apparatus (sa). The sa of the D1 spine is connected on adjacent sections to the tubule (small arrow); and this spine also contains a spherical vesicle (open arrow). The bouton presynaptic to the D2 spine wraps around the spine head so that the synapse appears on both sides in this section. The postsynaptic density is interrupted, or perforated, on one side (white arrowhead). In addition to the sa, the D2 spine contains a small clear profile (white arrow) found in series to be endosomal in nature. Both spines contain a floccular

cytoplasm (fc) consistent with an actin matrix. Symmetric shaft synapses (sym, white arrows) are present on D2 and D3. Next to the D3 symmetric synapse is a punctum adhaerens junction (pa). **(b)** Two dendrites (D1, D2) give rise to small spines with macular synapses (mac). The Spine of D2 has a spinule emerging from the edge of the synapse into the presynaptic axon. A third dendrite (D3) contains a vacuole (vac), which on serial section reconstruction is part of a macro-autophagosome. Scale bar in **(a)** is for **(a)** and **(b)**.

Fig. 1.13: Substructure of the postsynaptic density on dendritic spines. **(a)** 3DEM of a spine with a macular synapse on its head. The active zone (red) is adjacent to a large punctum adhaerens junction (blue). **(b)** A view of the synaptic face of a spine with a perforated postsynaptic density with a large active zone (red), three puncta adherens, (blue) and two vesicle-free transition zones (yellow). (rat; Spacek and Harris 1998) **(c)** Nascent zones (NZ) are the revised name for the vesicle-free transition zones. NZs have no presynaptic vesicles, thus distinguishing them from the active zone (AZ). **(d)** 3DEM of the docked vesicles (dark blue), and the adjacent (light gray) and distant (green) reserve pool vesicles, viewed on edge to reveal the nascent zones (turquoise) and active zones (red). **(e)** Identification and measurement of nascent zones in virtual sections from tilt tomography revealed vesicles, with some pressed against the AZ (blue arrows), but no vesicles above the NZ. **(f)** Stacked projection of the axon–spine interface (gray), AZ (red), and NZ (teal) that were first traced through the 2–3-nm virtual sections and then displayed orthogonal to the virtual section planes with white lines illustrating the locations of the virtual sections and F is equal to the virtual section in the micrograph of **(e)**. Maximum diameters of docked vesicles are illustrated as dark blue circles with scaled pores (yellow circles) circumscribed in vesicles that had them. Scale bar in **(f)** applies also to **(e)**. **(c-f** were adapted from Bell et al., 2014).

Fig. 1.14: Smooth endoplasmic reticulum in dendritic spines. **(a)** A cerebellar Purkinje cell spine showing the network of SER that extends into the spine from the dendrite. **(b)** The head of a neocortical mushroom spine containing a spine apparatus (sa) and polyribosomes (arrows). The lowest cluster of polyribosomes is located immediately adjacent to the sa, suggesting it may be rough endoplasmic reticulum. **(c)** High magnification image of the spine apparatus in a mushroom spine of the mouse visual cortex shows the inner dense plates between cisternae of SER. The electron-dense material reveals periodically organized granulofilamentous arrays in this tangential section. (reprinted with permission from Spacek 1985a.)

Fig. 1.15: Small thorny excrescence emerging from a thalamocortical relay neuron of the ventrobasal nucleus. **(a)** Electron micrograph of section through the excrescence. Beneath the synaptic lobe (asterisk) is a region (arrow) with a large number of polyribosomes. **(b)** 3DEM of the excrescence (gray) reveals the intense concentration of polyribosomes (black spheres) beneath the synapses (red).

Fig. 1.16: Perisynaptic structure of dendritic spines. **(a)** A spinule (arrow) extends into the presynaptic bouton from the middle of a perforated postsynaptic density on a dendritic spine of in adult rat CA1. (Harris and Stevens 1989) **(b)** 3DEM of spine with the same spinule (arrow). **(c)** An astrocytic process (black) contacts the edges of synapses onto two dendritic spines (s) in mouse cerebellar cortex. **(d)** 3DEM reveals that these two spines are completely enveloped by the astrocyte (translucent gray).

Fig. 1.17: Dendrites beaded by hydropic swelling. **(a)** Electron micrograph showing a segment of dendrite in human peritumorous neocortex in which two varicosities (asterisks) with watery cytoplasm are separated by a narrower region of denser cytoplasm. **(b)** Higher magnification of

the inter-varicosity region shows that it contains some vesicular components and microtubules and filaments that do not span the varicosities.

Fig. 1.18 Schematic of dendritic spine pathologies (Fiala et al., 2002b). **(a-f)** Pathologies of distribution as seen, for example, by light microscopy, involve differences from (a) normal spines by: (b) decreased density, (c) increased density, (d) reduction in spine size, (e) distortions of normal spine shapes, and (f) abnormally varicose dendrites that absorb spines. **(g-o)** Observed pathologies from (g) normal spine ultrastructure include: (h) shrunken spines with dense cytoplasm, (i) altered endoplasmic reticulum, (j) hypertrophied spine apparatus, (k) hypertrophied multivesicular bodies, (l) hypertrophied cytoskeleton, (m) spine microtubules, (n) giant spines, and (o) axonless spines with an axon-free postsynaptic density.

Reference List

Akert K, Pfenninger K, Sandri C (1967) Crest synapses with subjunctional bodies in the subfornical organ. Brain Res 5:118-120.

Altman J (1971) Coated vesicles and synaptogenesis. A developmental study in the cerebellar cortex of the rat. Brain Res 30:311-322.

Altman J, Bayer SA (1997) Development of the Cerebellar System: In Relation to Its Evolution, Structure, and Functions. Boca Raton, Florida: CRC Press.

Amaral DG, Witter MP (1989) The three-dimensional organization of the hippocampal formation: a review of anatomical data. Neurosci 31:571-591.

Anderson WA, Flumerfelt BA (1986a) A comparison of the effects of climbing fiber deafferentation in adult and weanling rats. Brain Res 383:228-244.

Anderson WA, Flumerfelt BA (1986b) Long-term effects of parallel fiber loss in the cerebellar cortex of the adult and weanling rat. Brain Res 383:245-261.

Angaut P, Sotelo C (1973) The fine structure of the cerebellar central nuclei in the cat. II. Synaptic organization. Exp Brain Res 16:431-454.

Applegate MD, Kerr DS, Landfield PW (1987) Redistribution of synaptic vesicles during long-term potentiation in the hippocampus. Brain Res 401:401-406.

Applegate MD, Landfield PW (1988) Synaptic vesicle redistribution during hippocampal frequency potentiation and depression in young and aged rats. J Neurosci 8:1096-1111.

Ascoli GA, et al. (2008) Petilla terminology: nomenclature of features of GABAergic interneurons of the cerebral cortex. Nat Rev Neurosci 9:557-568.

Bannister NJ, Larkman AU (1995a) Dendritic morphology of CA1 pyramidal neurones from the rat hippocampus: I. Branching patterns. J Comp Neurol 360:150-160.

Bannister NJ, Larkman AU (1995b) Dendritic morphology of CA1 pyramidal neurones from the rat hippocampus: II. Spine distributions. J Comp Neurol 360:161-171.

Banno T, Kohno K (1996) Conformational changes of smooth endoplasmic reticulum induced by brief anoxia in rat Purkinje cells. J Comp Neurol 369:462-471.

Bassell GJ, Zhang H, Byrd AL, Femino AM, Singer RH, Taneja KL, Lifshitz LM, Herman IM, Kosik KS (1998) Sorting of beta-actin mRNA and protein to neurites and growth cones in culture. J Neurosci 18:251-265.

Baude A, Nusser Z, Roberts JD, Mulvihill E, McIlhinney RA, Somogyi P (1993) The metabotropic glutamate receptor (mGluR1 alpha) is concentrated at perisynaptic membrane of neuronal subpopulations as detected by immunogold reaction. Neuron 11:771-787.

Beaulieu C, Colonnier M (1985) A laminar analysis of the number of round-asymmetrical and flat-symmetrical synapses on spines, dendritic trunks, and cell bodies in area 17 of the cat. J Comp Neurol 231:180-189.

Beck E, Bak IJ, Christ JF, Gajdusek DC, Gibbs CJ, Jr., Hassler R (1975) Experimental kuru in the spider monkey. Histopathological and ultrastructural studies of the brain during early stages of incubation. Brain 98:595-612.

Bell ME, Bourne JN, Chirillo MA, Mendenhall JM, Kuwajima M, Harris KM (2014) Dynamics of nascent and active zone ultrastructure as synapses enlarge during long-term potentiation in mature hippocampus. J Comp Neurol 522:3861-3884.

Bennett MV, Zukin RS (2004) Electrical coupling and neuronal synchronization in the Mammalian brain. Neuron 41:495-511.

Benson DL, Huntley GW (2010) Building and remodeling synapses. Hippocampus.

Bergles DE, Jahr CE (1997) Synaptic activation of glutamate transporters in hippocampal astrocytes. Neuron 19:1297-1308.

Bingol B, Sheng M (2011) Deconstruction for reconstruction: the role of proteolysis in neural plasticity and disease. Neuron 69:22-32.

Bourne J, Harris KM (2007) Do thin spines learn to be mushroom spines that remember? Curr Opin Neurobiol.

Bourne JN, Harris KM (2008) Balancing structure and function at hippocampal dendritic spines. Annu Rev Neurosci 31:47-67.

Bourne JN, Harris KM (2011a) Coordination of size and number of excitatory and inhibitory synapses results in a balanced structural plasticity along mature hippocampal CA1 dendrites during LTP. Hippocampus 21:354-373.

Bourne JN, Harris KM (2011b) Smooth endoplasmic reticulum scales with synapse size and number along mature CA1 dendrites during long-term potentiation.

Bourne JN, Harris KM (2012) Nanoscale analysis of structural synaptic plasticity. Curr Opin Neurobiol 22:372-382.

Bourne JN, Sorra KE, Hurlburt J, Harris KM (2007) Polyribosomes are increased in spines of CA1 dendrites 2 h after the induction of LTP in mature rat hippocampal slices. Hippocampus

17:1-4.

Caceres A, Steward O (1983) Dendritic reorganization in the denervated dentate gyrus of the rat following entorhinal cortical lesions: A golgi and electron microscopic analysis. J Comp Neurol 214:387-403.

Cameron HA, Kaliszewski CK, Greer CA (1991) Organization of mitochondria in olfactory bulb granule cell dendritic spines. Synapse 8:107-118.

Cauli B, Zhou X, Tricoire L, Toussay X, Staiger JF (2014) Revisiting enigmatic cortical calretinin-expressing interneurons. Front Neuroanat 8:52.

Chan-Palay V (1977) Cerebellar Dentate Nucleus: Organization, Cytology, and Transmitters. Berlin: Springer-Verlag.

Chan-Palay V, Palay SL, Billings-Gagliardi SM (1974) Meynert cells in the primate visual cortex. J Neurocytol 3:631-658.

Chang FL, Greenough WT (1982) Lateralized effects of monocular training on dendritic branching in adult split-brain rats. Brain Res 232:283-292.

Chen S, Hillman DE (1999) Dying-back of Purkinje cell dendrites with synapse loss in aging rats. J Neurocytol 28:187-196.

Chicurel ME, Harris KM (1989) Serial electron microscopy of CA3 dendritic spines synapsing with mossy fibers of rat hippocampus. Soc Neurosci Abs 15:256.

Chicurel ME, Harris KM (1992) Three-dimensional analysis of the structure and composition of CA3 branched dendritic spines and their synaptic relationships with mossy fiber boutons in the rat hippocampus. J Comp Neurol 325:169-182.

Chklovskii DB, Mel BW, Svoboda K (2004) Cortical rewiring and information storage. Nature 431:782-788.

Christie JM, Jahr CE (2006) Multivesicular release at Schaffer collateral-CA1 hippocampal synapses. J Neurosci 26:210-216.

Clarke LE, Barres BA (2013) Emerging roles of astrocytes in neural circuit development. Nat Rev Neurosci 14:311-321.

Colonnier M (1968) Synaptic patterns on different cell types in the different laminae of the cat visual cortex. An electron microscope study. Brain Res 9:268-287.

Cooney JR, Hurlburt JL, Selig DK, Harris KM, Fiala JC (2002) Endosomal compartments serve

multiple hippocampal dendritic spines from a widespread rather than a local store of recycling membrane. J Neurosci 22:2215-2224.

Cruz-Martin A, Crespo M, Portera-Cailliau C (2010) Delayed stabilization of dendritic spines in fragile X mice. J Neurosci 30:7793-7803.

Cuello AC (1983) Nonclassical neuronal communications. Fed Proc 42:2912-2922.

Cui-Wang T, Hanus C, Cui T, Helton T, Bourne J, Watson D, Harris KM, Ehlers MD (2012) Local zones of endoplasmic reticulum complexity confine cargo in neuronal dendrites. Cell 148:309-321.

Dailey ME, Smith SJ (1996) The dynamics of dendritic structure in developing hippocampal slices. J Neurosci 16:2983-2994.

De Robertis ED, Bennett HS (1955) Some features of the submicroscopic morphology of synapses in frog and earthworm. J Biophys Biochem Cytol 1:47-58.

De Zeeuw CI, Ruigrok TJ, Holstege JC, Jansen HG, Voogd J (1990) Intracellular labeling of neurons in the medial accessory olive of the cat: II. Ultrastructure of dendritic spines and their GABAergic innervation. J Comp Neurol 300:478-494.

Deller T, Orth CB, Del TD, Vlachos A, Burbach GJ, Drakew A, Chabanis S, Korte M, Schwegler H, Haas CA, Frotscher M (2007) A role for synaptopodin and the spine apparatus in hippocampal synaptic plasticity. Ann Anat 189:5-16.

Dent EW, Merriam EB, Hu X (2011) The dynamic cytoskeleton: backbone of dendritic spine plasticity. Curr Opin Neurobiol 21:175-181.

DiFiglia M, Carey J (1986) Large neurons in the primate neostriatum examined with the combined Golgi-electron microscopic method. J Comp Neurol 244:36-52.

Dunaevsky A, Tashiro A, Majewska A, Mason C, Yuste R (1999) Developmental regulation of spine motility in the mammalian central nervous system. PNAS 96:13438-13443.

Ebner FF, Colonnier M (1975) Synaptic patterns in the visual cortex of turtle: an electron microscopic study. J Comp Neurol 160:51-79.

Eccles JC, Ito M, Szentagothai J (1967) The Cerebellum as a Neuronal Machine. New York/Heidelberg: Springer-Verlag.

Ehlers MD (2013) Dendritic trafficking for neuronal growth and plasticity. Biochem Soc Trans 41:1365-1382.

Ellias SA, Stevens JK (1980) The dendritic varicosity: a mechanism for electrically isolating the

dendrites of cat retinal amacrine cells? Brain Res 196:365-372.

Fannon AM, Colman DR (1996) A model for central synaptic junctional complex formation based on the differential adhesive specificities of the cadherins. Neuron 17:423-434.

Feldman ML, Peters A (1978) The forms of non-pyramidal neurons in the visual cortex of the rat. J Comp Neurol 179:761-793.

Fernández E, Jelinek HF (2001) Use of fractal theory in neuroscience: methods, advantages, and potential problems. Methods 24:309-321.

Fiala JC, Allwardt B, Harris KM (2002a) Dendritic spines do not split during hippocampal LTP or maturation. Nat Neurosci 5:297-298.

Fiala JC, Feinberg M, Popov V, Harris KM (1998) Synaptogenesis via dendritic filopodia in developing hippocampal area CA1. J Neurosci 18:8900-8911.

Fiala JC, Kirov SA, Feinberg MD, Petrak LJ, George P, Goddard CA, Harris KM (2003) Timing of neuronal and glial ultrastructure disruption during brain slice preparation and recovery in vitro. J Comp Neurol 465:90-103.

Fiala JC, Spacek J, Harris KM (2002b) Dendritic spine pathology: cause or consequence of neurological disorders? Brain Res Brain Res Rev 39:29-54.

Fields RD, Itoh K (1996) Neural cell adhesion molecules in activity-dependent development and synaptic plasticity. Trends Neurosci 19:473-480.

Fifkova E (1985) A possible mechanism of morphometric changes in dendritic spines induced by stimulation. Cell Mol Neurobiol 5:47-63.

Fischer M, Kaech S, Knutti D, Matus A (1998) Rapid actin-based plasticity in dendritic spines. Neuron 20:847-854.

Floris A, Dino M, Jacobowitz DM, Mugnaini E (1994) The unipolar brush cells of the rat cerebellar cortex and cochlear nucleus are calretinin-positive: a study by light and electron microscopic immunocytochemistry. Anat Embryol (Berl) 189:495-520.

Franks KM, Bartol TM, Jr., Sejnowski TJ (2002) A Monte Carlo model reveals independent signaling at central glutamatergic synapses. Biophys J 83:2333-2348.

Franks KM, Stevens CF, Sejnowski TJ (2003) Independent sources of quantal variability at single glutamatergic synapses. J Neurosci 23:3186-3195.

Freund TF, Powell JF, Smith AD (1984) Tyrosine hydroxylase-immunoreactive boutons in

synaptic contact with identified striatonigral neurons, with particular reference to dendritic spines. Neurosci 13:1189-1215.

Fridtjof Nansen (1887) The Structure and Combination of the Histological Elements of the Central Nervous System. Bergens Museums Aarsberetning for 1886.

Fukuda Y, Hsiao CF, Watanabe M, Ito H (1984) Morphological correlates of physiologically identified Y-, X-, and W-cells in cat retina. J Neurophysiol 52:999-1013.

Geinisman Y, deToledo-Morrell L, Morrell F, Persina IS, Beatty MA (1996) Synapse restructuring associated with the maintenance phase of hippocampal long-term potentiation. J Comp Neurol 368:413-423.

Geinisman Y, Morrell F, de Toledo-Morrell L (1987) Axospinous synapses with segmented postsynaptic densities: a morphologically distinct synaptic subtype contributing to the number of profiles of 'perforated' synapses visualized in random sections. Brain Res 423:179-188.

Globus A (1975) Brain morphology as a function of presynaptic morphology and activity. In: Dev. Neuropsychol. of Sensory Deprivation (Reisen H, ed), pp 9-91. New York: Academic Press.

Golgi C (1908) La doctrine du neurone, théorie et faits. In: Les prix Nobel 1906 (Hasselberg KB, Petterson SO, Mörner KAH, Wirsén CD, Santesson MCG, eds), pp 1-31. Stockholm: Imprimerie Royale, Norstedt & Söner.

Graveland GA, Williams RS, DiFiglia M (1985) Evidence for degenerative and regenerative changes in neostriatal spiny neurons in Huntington's disease. Science 227:770-773.

Gray EG (1959) Axo-somatic and axo-dendritic synapses of the cerebral cortex: an electron microscope study. J Anat 93:420-433.

Gray EG (1982) Rehabilitating the dendritic spine. Trends Neurosci 5:5-6.

Greenough WT, Volkmar FR, Juraska JM (1973) Effects of rearing complexity on dendritic branching in frontolateral and temporal cortex of the rat. Exp Neurol 41:371-378.

Grutzendler J, Kasthuri N, Gan WB (2002) Long-term dendritic spine stability in the adult cortex. Nature 420:812-816.

Gu J, Firestein BL, Zheng JQ (2008) Microtubules in dendritic spine development. J Neurosci 28:12120-12124.

Guillery RW (2005) Observations of synaptic structures: origins of the neuron doctrine and its current status. Philos Trans R Soc Lond B Biol Sci 360:1281-1307.

Halpain S, Hipolito A, Saffer L (1998) Regulation of F-actin stability in dendritic spines by glutamate receptors and calcineurin. J Neurosci 18:9835-9844.

Hama K, Arii T, Kosaka T (1994) Three-dimensional organization of neuronal and glial processes: high voltage electron microscopy. Microsc Res Tech 29:357-367.

Harris KM (1999) Structure, development, and plasticity of dendritic spines. Curr Opin Neurobiol 9:343-348.

Harris KM, Bourne JN, Mendenhall JM, Spacek J (2007) Hippocampal CA1 dendrites of greater caliber have more spines and contain more microtubules as a subcellular supply route.

Harris KM, Jensen FE, Tsao B (1992) Three-dimensional structure of dendritic spines and synapses in rat hippocampus (CA1) at postnatal day 15 and adult ages: implications for the maturation of synaptic physiology and long-term potentiation. J Neurosci 12:2685-2705.

Harris KM, Kater SB (1994) Dendritic spines: cellular specializations imparting both stability and flexibility to synaptic function. Annu Rev Neurosci 17:341-371.

Harris KM, Landis DM (1986) Membrane structure at synaptic junctions in area CA1 of the rat hippocampus. Neurosci 19:857-872.

Harris KM, Marshall PE, Landis DM (1985) Ultrastructural study of cholecystokinin-immunoreactive cells and processes in area CA1 of the rat hippocampus. J Comp Neurol 233:147-158.

Harris KM, Spacek J (1995) Three-dimensional organization of SER and other organelles in dendritic spines of rat hippocampus (CA1). pp 594.

Harris KM, Stevens JK (1988a) Dendritic spines of rat cerebellar Purkinje cells: serial electron microscopy with reference to their biophysical characteristics. J Neurosci 8:4455-4469.

Harris KM, Stevens JK (1988b) Study of dendritic spines by serial electron microscopy and three-dimensional reconstructions. In: Intrinsic determinants of neuronal form and function. Neurology and Neurobiology Volume 37 (Lasek RJ, Black MM, eds), pp 179-199. New York: Alan R. Liss.

Harris KM, Stevens JK (1989) Dendritic spines of CA1 pyramidal cells in the rat hippocampus: serial electron microscopy with reference to their biophysical characteristics. J Neurosci 9:2982-2997.

Harris KM, Weinberg RJ (2012) Ultrastructure of synapses in the mammalian brain. Cold Spring Harb Perspect Biol 4.

Harvey RJ, Napper RM (1991) Quantitative studies on the mammalian cerebellum. Prog Neurobiol 36:437-463.

Henkart M, Landis DM, Reese TS (1976) Similarity of junctions between plasma membranes and endoplasmic reticulum in muscle and neurons. J Cell Biol 70:338-347.

Higley MJ, Sabatini BL (2008) Calcium signaling in dendrites and spines: practical and functional considerations. Neuron 59:902-913.

Hirano A (1981) A guide to neuropathology. New York, NY, Tokyo, Japan: Igaku-Shoin.

Holderith N, Lorincz A, Katona G, Rozsa B, Kulik A, Watanabe M, Nusser Z (2012) Release probability of hippocampal glutamatergic terminals scales with the size of the active zone. Nat Neurosci 15:988-997.

Horton AC, Ehlers MD (2003) Dual modes of endoplasmic reticulum-to-Golgi transport in dendrites revealed by live-cell imaging. J Neurosci 23:6188-6199.

Horton AC, Ehlers MD (2004) Secretory trafficking in neuronal dendrites. Nat Cell Biol 6:585-591.

Horton AC, Racz B, Monson EE, Lin AL, Weinberg RJ, Ehlers MD (2005) Polarized secretory trafficking directs cargo for asymmetric dendrite growth and morphogenesis. Neuron 48:757-771.

Hrycyshyn AW, Flumerfelt BA (1981a) A light microscopic investigation of the afferent connections of the lateral reticular nucleus in the cat. J Comp Neurol 197:477-502.

Hrycyshyn AW, Flumerfelt BA (1981b) An electron microscopic study of the afferent connections of the lateral reticular nucleus of the cat. J Comp Neurol 197:503-516.

Hrycyshyn AW, Flumerfelt BA (1981c) Cytology and synaptology of the lateral reticular nucleus of the cat. J Comp Neurol 197:459-475.

Hu X, Viesselmann C, Nam S, Merriam E, Dent EW (2008) Activity-dependent dynamic microtubule invasion of dendritic spines. J Neurosci 28:13094-13105.

Humeau Y, Herry C, Kemp N, Shaban H, Fourcaudot E, Bissiere S, Luthi A (2005) Dendritic spine heterogeneity determines afferent-specific Hebbian plasticity in the amygdala. Neuron 45:119-131.

Jacobs B, Batal HA, Lynch B, Ojemann G, Ojemann LM, Scheibel AB (1993) Quantitative dendritic and spine analyses of speech cortices: a case study. Brain Lang 44:239-253.

Jaworski J, Kapitein LC, Gouveia SM, Dortland BR, Wulf PS, Grigoriev I, Camera P, Spangler

SA, Di SP, Demmers J, Krugers H, Defilippi P, Akhmanova A, Hoogenraad CC (2009) Dynamic microtubules regulate dendritic spine morphology and synaptic plasticity. Neuron 61:85-100.

Jones DG, Harris RJ (1995) An analysis of contemporary morphological concepts of synaptic remodelling in the CNS: perforated synapses revisited. Rev Neurosci 6:177-219.

Jones EG (1975) Varieties and distribution of non-pyramidal cells in the somatic sensory cortex of the squirrel monkey. J Comp Neurol 160:205-267.

Jones EG, Powell TP (1969) Morphological variations in the dendritic spines of the neocortex. J Cell Sci 5:509-529.

Kaufmann WE, Moser HW (2000) Dendritic anomalies in disorders associated with mental retardation. Cereb Cortex 10:981-991.

Kennedy MB (2000) Signal-processing machines at the postsynaptic density. Science 290:750-754.

Kennedy MJ, Davison IG, Robinson CG, Ehlers MD (2010) Syntaxin-4 defines a domain for activity-dependent exocytosis in dendritic spines. Cell 141:524-535.

Kishi K, Mori K, Tazawa Y (1982) Three-dimensional analysis of dendritic trees of mitral cells in the rabbit olfactory bulb. Neurosci Lett 28:127-132.

Klopfenstein DR, Kappeler F, Hauri HP (1998) A novel direct interaction of endoplasmic reticulum with microtubules. EMBO J 17:6168-6177.

Kniffki KD, Pawlak M, Vahle-Hinz C (1994) Fractal Dimensions and Dendritic Branching of Neurons in the Somatosensory Thalamus. In: Fractals in Biology and Medicine (Nonnenmacher TF, Losa GA, Weibel ER, eds), pp 221-229. Basel: Birkhäuser.

Kolb H, Fernández E, Schouten J, Ahnelt P, Linberg KA, Fisher SK (1994) Are there three types of horizontal cell in the human retina? J Comp Neurol 343:370-386.

Kolb H, Linberg KA, Fisher SK (1992) Neurons of the human retina: a Golgi study. J Comp Neurol 318:147-187.

Kraev IV, Godukhin OV, Patrushev IV, Davies HA, Popov VI, Stewart MG (2009) Partial kindling induces neurogenesis, activates astrocytes and alters synaptic morphology in the dentate gyrus of freely moving adult rats. Neurosci 162:254-267.

Krichevsky AM, Kosik KS (2001) Neuronal RNA granules: a link between RNA localization and stimulation- dependent translation. Neuron 32:683-696.

Kruger L, Otis TS (2007) Whither withered Golgi? A retrospective evaluation of reticularist and synaptic constructs. Brain Res Bull 72:201-207.

Kuwajima M, Spacek J, Harris KM (2013) Beyond counts and shapes: Studying pathology of dendritic spines in the context of the surrounding neuropil through serial section electron microscopy. Neurosci 251:75-89.

Larkman AU (1991) Dendritic morphology of pyramidal neurones of the visual cortex of the rat: III. Spine distributions. J Comp Neurol 306:332-343.

Lenn NJ (1976) Synapses in the interpeduncular nucleus: electron microscopy of normal and habenula lesioned rats. J Comp Neurol 166:77-99.

Li Z, Okamoto K, Hayashi Y, Sheng M (2004) The importance of dendritic mitochondria in the morphogenesis and plasticity of spines and synapses. Cell 119:873-887.

Lieberman AR (1973) Neurons with presynaptic perikarya and presynaptic dendrites in the rat lateral geniculate nucleus. Brain Res 59:35-59.

Lieberman AR, Spacek J (1997) Filamentous contacts: the ultrastructure and three-dimensional organization of specialized non-synaptic interneuronal appositions in thalamic relay nuclei. Cell Tissue Res 288:43-57.

Lisman J, Harris KM (1993) Quantal analysis and synaptic anatomy - integrating two views of hippocampal plasticity. Trends Neurosci 16:141-147.

Lu J, Helton TD, Blanpied TA, Racz B, Newpher TM, Weinberg RJ, Ehlers MD (2007) Postsynaptic positioning of endocytic zones and AMPA receptor cycling by physical coupling of dynamin-3 to Homer. Neuron 55:874-889.

Luscher C, Nicoll RA, Malenka RC, Muller D (2000) Synaptic plasticity and dynamic modulation of the postsynaptic membrane. Nat Neurosci 3:545-550.

Luthl A, Laurent JP, Figurov A, Muller D, Schachner M (1994) Hippocampal long-term potentiation and neural cell adhesion molecules L1 and NCAM. Nature 372:777-779.

MacGillavry HD, Song Y, Raghavachari S, Blanpied TA (2013) Nanoscale scaffolding domains within the postsynaptic density concentrate synaptic AMPA receptors. Neuron 78:615-622.

MacNeil MA, Masland RH (1998) Extreme diversity among amacrine cells: implications for function. Neuron 20:971-982.

Magistretti PJ, Pellerin L, Rothman DL, shulman RG (1999) Energy on Demand. Science 283:496-497.

Majewski L, Kuznicki J (2015) SOCE in neurons: Signaling or just refilling? Biochim Biophys Acta.

Mariani AP (1990) Amacrine cells of the rhesus monkey retina. J Comp Neurol 301:382-400.

Marrs GS, Green SH, Dailey ME (2001) Rapid formation and remodeling of postsynaptic densities in developing dendrites. Nat Neurosci 4:1006-1013.

Martone ME, Zhang Y, Simpliciano VM, Carragher BO, Ellisman MH (1993) Three-dimensional visualization of the smooth endoplasmic reticulum in Purkinje cell dendrites. Journal of Neuroscience 13:4636-4646.

Matsuzaki M, Ellis-Davies GC, Nemoto T, Miyashita Y, Iino M, Kasai H (2001) Dendritic spine geometry is critical for AMPA receptor expression in hippocampal CA1 pyramidal neurons. Nat Neurosci 4:1086-1092.

McBrayer M, Nixon RA (2013) Lysosome and calcium dysregulation in Alzheimer's disease: partners in crime. Biochem Soc Trans 41:1495-1502.

McWilliams JR, Lynch G (1981) Sprouting in the hippocampus is accompanied by an increase in coated vesicles. Brain Res 211:158-164.

Megias M, Emri Z, Freund TF, Gulyas AI (2001) Total number and distribution of inhibitory and excitatory synapses on hippocampal CA1 pyramidal cells. Neurosci 102:527-540.

Milhaud M, Pappas GD (1966) The fine structure of neurons and synapses of the habenula of the cat with special reference to subjunctional bodies. Brain Res 3:158-173.

Mishchenko Y, Hu T, Spacek J, Mendenhall J, Harris KM, Chklovskii DB (2010) Ultrastructural analysis of hippocampal neuropil from the connectomics perspective. Neuron 67:1009-1020.

Morest DK (1969) The differentiation of cerebral dendrites: A study of the post-migratory neuroblast in the medial nucleus of the trapezoid body. Z Anat Entwicklungsgesch 128:271-289.

Mugnaini E, Floris A (1994) The unipolar brush cell: a neglected neuron of the mammalian cerebellar cortex. J Comp Neurol 339:174-180.

Mugnaini E, Floris A, Wright-Goss M (1994) Extraordinary synapses of the unipolar brush cell: an electron microscopic study in the rat cerebellum. Synapse 16:284-311.

Muller D, Wang C, Skibo G, Toni N, Cremer H, Calaora V, Rougon G, Kiss JZ (1996) PSA-NCAM is required for activity-induced synaptic plasticity. Neuron 17:413-422.

Nafstad PH, Blackstad TW (1966) Distribution of mitochondria in pyramidal cells and boutons in hippocampal cortex. Z Zellforsch Mikrosk Anat 73:234-245.

Nair D, Hosy E, Petersen JD, Constals A, Giannone G, Choquet D, Sibarita JB (2013) Super-resolution imaging reveals that AMPA receptors inside synapses are dynamically organized in nanodomains regulated by PSD95. J Neurosci 33:13204-13224.

Napper RM, Harvey RJ (1988a) Number of parallel fiber synapses on an individual Purkinje cell in the cerebellum of the rat. J Comp Neurol 274:168-177.

Napper RM, Harvey RJ (1988b) Quantitative study of the Purkinje cell dendritic spines in the rat cerebellum. J Comp Neurol 274:158-167.

Nicholson DA, Geinisman Y (2009) Axospinous synaptic subtype-specific differences in structure, size, ionotropic receptor expression, and connectivity in apical dendritic regions of rat hippocampal CA1 pyramidal neurons. J Comp Neurol 512:399-418.

Nicholson DA, Trana R, Katz Y, Kath WL, Spruston N, Geinisman Y (2006) Distance-dependent differences in synapse number and AMPA receptor expression in hippocampal CA1 pyramidal neurons. Neuron 50:431-442.

Nixon RA (2007) Autophagy, amyloidogenesis and Alzheimer disease. J Cell Sci 120:4081-4091.

Nixon RA (2013) The role of autophagy in neurodegenerative disease. Nat Med 19:983-997.

Nusser Z (2000) AMPA and NMDA receptors: similarities and differences in their synaptic distribution. Curr Opin Neurobiol 10:337-341.

Ostapoff EM, Feng JJ, Morest DK (1994) A physiological and structural study of neuron types in the cochlear nucleus. II. Neuron types and their structural correlation with response properties. J Comp Neurol 346:19-42.

Ostroff LE, Fiala JC, Allwardt B, Harris KM (2002) Polyribosomes redistribute from dendritic shafts into spines with enlarged synapses during LTP in developing rat hippocampal slices. Neuron 35:535-545.

Overly CC, Rieff HI, Hollenbeck PJ (1996) Organelle motility and metabolism in axons vs dendrites of cultured hippocampal neurons. J Cell Sci 109 (Pt 5):971-980.

Palade GE, Palay SL (1954) Electron microscopic observations of interneuronal and neuromuscular synapses. Anat Rec 118:335-336.

Palay SL, Chan-Palay V (1974) Cerebellar cortex: cytology and organization. New York: Springer-Verlag.

Panico J, Sterling P (1995) Retinal neurons and vessels are not fractal but space-filling. J Comp Neurol 361:479-490.

Park M, Salgado JM, Ostroff L, Helton TD, Robinson CG, Harris KM, Ehlers MD (2006) Plasticity-induced growth of dendritic spines by exocytic trafficking from recycling endosomes. Neuron 52:817-830.

Parra P, Gulyas AI, Miles R (1998) How many subtypes of inhibitory cells in the hippocampus? Neuron 20:983-993.

Peters A (2002) Structural changes in the normally aging cerebral cortex of primates. Prog Brain Res 136:455-465.

Peters A, Kaiserman-Abramof IR (1970) The small pyramidal neuron of the rat cerebral cortex. The perikaryon, dendrites and spines. Am J Anat 127:321-355.

Peters A, Palay SL (1996) The morphology of synapses. J Neurocytol 25:687-700.

Pierce JP, Mayer T, McCarthy JB (2001) Evidence for a satellite secretory pathway in neuronal dendritic spines. Curr Biol 11:351-355.

Pierce JP, van Leyen K, McCarthy JB (2000) Translocation machinery for synthesis of integral membrane and secretory proteins in dendritic spines. Nat Neurosci 3:311-313.

Popov V, Medvedev NI, Davies HA, Stewart MG (2005) Mitochondria form a filamentous reticular network in hippocampal dendrites but are present as discrete bodies in axons: a three-dimensional ultrastructural study. J Comp Neurol 492:50-65.

Popov VI, Medvedev NI, Rogachevskii VV, Ignat'ev DA, Stewart MG, Fesenko EE (2003) [Three-dimentional organization of synapses and astroglia in the hippocampus of rats and ground squirrels: new structural and functional paradigms of the synapse function]. Biofizika 48:289-308.

Porter R, Ghosh S, Lange GD, Smith TG, Jr. (1991) A fractal analysis of pyramidal neurons in mammalian motor cortex. Neurosci Lett 130:112-116.

Portera-Cailliau C (2012) Which comes first in fragile X syndrome, dendritic spine dysgenesis or defects in circuit plasticity? Neuroscientist 18:28-44.

Price JL, Powell TP (1970) The synaptology of the granule cells of the olfactory bulb. J Cell Sci 7:125-155.

Prieto JJ, Winer JA (1999) Layer VI in cat primary auditory cortex: Golgi study and sublaminar origins of projection neurons. J Comp Neurol 404:332-358.

Purves D, Snider WD, Voyvodic JT (1988) Trophic regulation of nerve cell morphology and innervation in the autonomic nervous system. Nature 336:123-128.

Racz B, Blanpied TA, Ehlers MD, Weinberg RJ (2004) Lateral organization of endocytic machinery in dendritic spines. Nat Neurosci 7:917-918.

Raghavachari S, Lisman JE (2004) Properties of quantal transmission at CA1 synapses. J Neurophysiol 92:2456-2467.

Ramón y Cajal S (1991) Degeneration and regeneration of the nervous system. New York: Oxford University Press.

Ramon Y Cajal S (1954) Neuron Theory or Reticular theory. English Translation. (Purkiss MU, Fox CA, eds), Madrid: Consejo Superior De Investigaciones Cientificas.

Ramon Y Cajal S (1995) Histology of the Nervous System, English Translation. New York: Oxford University Press.

Rámon Y Cajal S (1995) Histology of the Nervous System, English Translation. New York: Oxford University Press.

Ramón-Moliner E (1968) The morphology of dendrites. In: The Structure and Function of Nervous Tissue (Bourne GH, ed), pp 205-267. New York: Academic Press.

Richards DA, Mateos JM, Hugel S, De Paola V, Caroni P, Gahwiler BH, McKinney RA (2005) Glutamate induces the rapid formation of spine head protrusions in hippocampal slice cultures. Proc Natl Acad Sci U S A 102:6166-6171.

Rollenhagen A, Satzler K, Rodriguez EP, Jonas P, Frotscher M, Lubke JH (2007) Structural determinants of transmission at large hippocampal mossy fiber synapses. J Neurosci 27:10434-10444.

Ruigrok TJ, De Zeeuw CI, van der Burg J, Voogd J (1990) Intracellular labeling of neurons in the medial accessory olive of the cat: I. Physiology and light microscopy. J Comp Neurol 300:462-477.

Scheibel AB (1982) Age-related changes in the human forebrain. Neurosci Res Program Bull 20:577-583.

Scheibel ME, Lindsay RD, Tomiyasu U, Scheibel AB (1975) Progressive dendritic changes in aging human cortex. Exp Neurol 47:392-403.

Scheibel ME, Scheibel AB (1977) Specific postnatal threats to brain development: Dendritic changes. In: Brain: Fetal and Infant: Current Research on Normal and Abnomal development (Berenberg SR, ed), pp 302-315. The Hague: Martinus Nijhoff Medical Division.

Schikorski T, Stevens CF (2001) Morphological correlates of functionally defined synaptic vesicle populations. Nat Neurosci 4:391-395.

Scorcioni R, Lazarewicz MT, Ascoli GA (2004) Quantitative morphometry of hippocampal pyramidal cells: differences between anatomical classes and reconstructing laboratories. J Comp Neurol 473:177-193.

Shepherd GM (1991) Foundations of the Neuron Doctrine. New York: Oxford University Press.

Shepherd GM, Harris KM (1998) Three-dimensional structure and composition of CA3-->CA1 axons in rat hippocampal slices: implications for presynaptic connectivity and compartmentalization. J Neurosci 18:8300-8310.

Sholl DA (1953) Dendritic organization in the neurons of the visual and motor cortices of the cat. J Anat 87:387-406.

Sholl DA (1967) The Organization of the Cerebral Cortex. New York: Hafner Publishing Company.

Sloper JJ, Powell TP (1978) Dendro-dendritic and reciprocal synapses in the primate motor cortex. Proc R Soc Lond B Biol Sci 203:23-38.

Smith TG, Jr., Marks WB, Lange GD, Sheriff WH, Jr., Neale EA (1989) A fractal analysis of cell images. J Neurosci Methods 27:173-180.

Sorra KE, Fiala JC, Harris KM (1998) Critical assessment of the involvement of perforations, spinules, and spine branching in hippocampal synapse formation. J Comp Neurol 398:225-240.

Sorra KE, Harris KM (1993) Occurrence and three-dimensional structure of multiple synapses between individual radiatum axons and their target pyramidal cells in hippocampal area CA1. J Neurosci 13:3736-3748.

Sotelo C, Angaut P (1973) The fine structure of the cerebellar central nuclei in the cat. I. Neurons and neuroglial cells. Exp Brain Res 16:410-430.

Spacek J (1982) 'Free' postsynaptic-like densities in normal adult brain: their occurrence, distribution, structure and association with subsurface cisterns. J Neurocytol 11:693-706.

Spacek J (1985a) Three-dimensional analysis of dendritic spines. II. Spine apparatus and other cytoplasmic components. Anat Embryol (Berl) 171:235-243.

Spacek J (1985b) Three-dimensional analysis of dendritic spines. III. Glial sheath. Anat Embryol (Berl) 171:245-252.

Spacek J (1987) Ultrastructural pathology of dendritic spines in epitumorous human cerebral cortex. Acta Neuropathol 73:77-85.

Spacek J, Harris KM (1997) Three-dimensional organization of smooth endoplasmic reticulum in hippocampal CA1 dendrites and dendritic spines of the immature and mature rat. J Neurosci 17:190-203.

Spacek J, Harris KM (1998) Three-dimensional organization of cell adhesion junctions at synapses and dendritic spines in area CA1 of the rat hippocampus. J Comp Neurol 393:58-68.

Spacek J, Harris KM (2004) Trans-endocytosis via spinules in adult rat hippocampus. J Neurosci 24:4233-4241.

Spacek J, Hartmann M (1983) Three-dimensional analysis of dendritic spines. I. Quantitative observations related to dendritic spine and synaptic morphology in cerebral and cerebellar cortices. Anat Embryol (Berl) 167:289-310.

Spacek J, Lieberman AR (1974) Ultrastructure and three-dimensional organization of synaptic glomeruli in rat somatosensory thalamus. J Anat 117:487-516.

Spacek J, Lieberman AR (1980) Relationships between mitochondrial outer membranes and agranular reticulum in nervous tissue: ultrastructural observations and a new interpretation. J Cell Sci 46:129-147.

Stepanyants A, Hof PR, Chklovskii DB (2002) Geometry and structural plasticity of synaptic connectivity. Neuron 34:275-288.

Sterling P (1990) Retina. In: The Synaptic Organization of the Brain (Shepherd GM, ed), New York: Oxford University Press.

Steward O, Falk PM, Torre ER (1996) Ultrastructural basis for gene expression at the synapse: synapse-associated polyribosome complexes. J Neurocytol 25:717-734.

Stoyanova I, Dandov A, Lazarov N, Chouchkov C (1998) GABA- and glutamate-immunoreactivity in sensory ganglia of cat: a quantitative analysis. Arch Physiol Biochem 106:362-369.

Swindale NV (1981) Dendritic Spines only connect. Trends Neurosci 4:240-242.

Takeda T, Ishikawa A, Ohtomo K, Kobayashi Y, Matsuoka T (1992) Fractal dimension of dendritic tree of cerebellar Purkinje cell during onto- and phylogenetic development. Neurosci Res 13:19-31.

Tanaka J, Matsuzaki M, Tarusawa E, Momiyama A, Molnar E, Kasai H, Shigemoto R (2005) Number and density of AMPA receptors in single synapses in immature cerebellum. J Neurosci

25:799-807.

Tang L, Hung CP, Schuman EM (1998) A role for the cadherin family of cell adhesion molecules in hippocampal long-term potentiation. Neuron 20:1165-1175.

Tao-Cheng JH, Vinade L, Smith C, Winters CA, Ward R, Brightman MW, Reese TS, Dosemeci A (2001) Sustained elevation of calcium induces Ca(2+)/calmodulin-dependent protein kinase II clusters in hippocampal neurons. Neurosci 106:69-78.

Tarrant SB, Routtenberg A (1977) The synaptic spinule in the dendritic spine: Electron microscopic study of the hippocampal dentate gyrus. Tissue Cell 9:461-473.

Trommald M, Hulleberg G (1997) Dimensions and density of dendritic spines from rat dentate granule cells based on reconstructions from serial electron micrographs. J Comp Neurol 377:15-28.

Trommald M, Jensen V, Andersen P (1995) Analysis of dendritic spines in rat CA1 pyramidal cells intracellularly filled with a fluorescent dye. J Comp Neurol 353:260-274.

Uchida N, Honjo Y, Johnson KR, Wheelock MJ, Takeichi M (1996) The catenin/cadherin adhesion system is localized in synaptic junctions bordering transmitter release zones. J Cell Biol 135:767-779.

Ulfhake B, Kellerth JO (1981) A quantitative light microscopic study of the dendrites of cat spinal alpha-motoneurons after intracellular staining with horseradish peroxidase. J Comp Neurol 202:571-583.

Uylings HB, van PJ (2002) Measures for quantifying dendritic arborizations. Network 13:397-414.

Vedrenne C, Klopfenstein DR, Hauri HP (2005) Phosphorylation controls CLIMP-63-mediated anchoring of the endoplasmic reticulum to microtubules. Mol Biol Cell 16:1928-1937.

Ventura R, Harris KM (1998) Many hippocampal synapses have astrocytic processes at their perimeter where glutamate could be detected and spillover limited. Submitted.

Volkmar FR, Greenough WT (1972) Rearing complexity affects branching of dendrites in the visual cortex of the rat. Science 176:1445-1447.

Ward R, Moreau B, Marchand MJ, Garenc C (1995) A note on the distribution of dendritic spines. J Hirnforsch 36:519-522.

Westrum LE, Blackstad TW (1962) An electron microscopic study of the stratum radiatum of the rat hippocampus (regio superior, CA 1) with particular emphasis on synaptology. J Comp

Neurol 119:281-309.

Westrum LE, Gray EG (1977) Microtubules associated with postsynaptic 'thickenings'. J Neurocytol 6:505-518.

Westrum LE, Jones DH, Gray EG, Barron J (1980) Microtubules, dendritic spines and spine apparatuses. Cell Tissue Res 208:171-181.

Wilson CJ, Groves PM, Kitai ST, Linder JC (1983) Three dimensional structure of dendritic spines in rat striatum. J Neurosci 3:383-398.

Wilson JR, Friedlander MJ, Sherman SM (1984) Fine structural morphology of identified X- and Y-cells in the cat's lateral geniculate nucleus. Proc R Soc Lond B Biol Sci 221:411-436.

Wingate RJ, Fitzgibbon T, Thompson ID (1992) Lucifer yellow, retrograde tracers, and fractal analysis characterise adult ferret retinal ganglion cells. J Comp Neurol 323:449-474.

Witcher MR, Park YD, Lee MR, Sharma S, Harris KM, Kirov SA (2010) Three-dimensional relationships between perisynaptic astroglia and human hippocampal synapses. Glia 58:572-587.

Wolfe DM, Lee JH, Kumar A, Lee S, Orenstein SJ, Nixon RA (2013) Autophagy failure in Alzheimer's disease and the role of defective lysosomal acidification. Eur J Neurosci 37:1949-1961.

Xu-Friedman MA, Harris KM, Regehr WG (2001) Three-dimensional comparison of ultrastructural characteristics at depressing and facilitating synapses onto cerebellar Purkinje cells. J Neurosci 21:6666-6672.

Yelnik J, Percheron G, Francois C (1984) A Golgi analysis of the primate globus pallidus. II. Quantitative morphology and spatial orientation of dendritic arborizations. J Comp Neurol 227:200-213.

Yuan A, Rao MV, Veeranna, Nixon RA (2012) Neurofilaments at a glance. J Cell Sci 125:3257-3263.

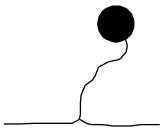
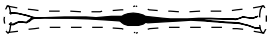
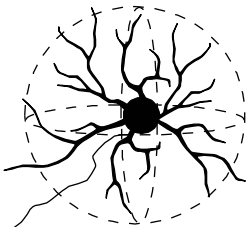
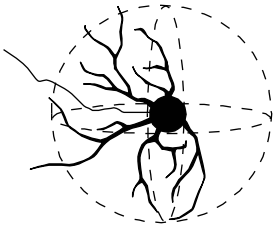
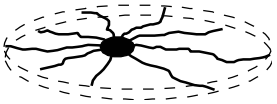
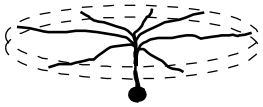
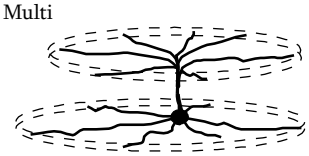
Yuste R (2013) Electrical compartmentalization in dendritic spines. Annu Rev Neurosci 36:429-449.

Table 1.1 Typical dimensions of dendrites for a few types of neurons

Neuron	Average soma diameter (μm)	Number of dendrites at soma	Proximal dendrite diameter (μm)	Number of branch points	Distal dendrite diameter (μm)	Dendrite extent* (μm)	Total dendritic length (μm)
Cerebellar granule cell (cat)	7	4	1	0	0.2-2	15	60
Starburst amacrine cell (rhesus)	9	1	1	40	0.2-2	120	—
Dentate gyrus granule cell (rat)	14	2	3	14	0.5-1	300	3200
CA1 pyramidal cell (rat)	21						11 900
basal dendrites		5	1	30	0.5-1	130	5500
stratum radiatum		1	3	30	0.25-1	110	4100
stratum lacunosum-moleculare				15	0.25-1	500	2300
Cerebellar Purkinje cell (guinea pig)	25	1	3	440	0.8-2.2	200	9100
Principal cell of globus pallidus (human)	33	4	4	12	0.3-0.5	1000	7600
Meynert cell of visual cortex (macaque)	35						15 400
basal dendrites		5	3	—	—	250	10 200
apical dendrites		1	4	15	2-3	1800	5200
Spinal α-motoneuron (cat)	58	11	8	120	0.5-1.5	1100	52 000

* The average distance from the cell body to the tips of the longest dendrites.
Sources: Ito (1984); Mariani (1990); Claiborne *et al.* (1990); Bannister and Larkman (1995a); Rapp *et al.* (1994); Palay (1978); Yelnik *et al.* (1984); Ulfhake and Kellerth (1981)

Table 1.2 Some characteristic dendritic arborization patterns

Pattern	Characteristics	Examples
Adendritic 	Cell body lacks dendrites	Dorsal root ganglion cells Sympathetic ganglion cells
Spindle radiation 	Two dendrites emerge from opposite poles of the cell body and have few branches	Lugaro cells Bipolar cells of cortex
Spherical radiation		
Stellate 	Dendrites radiate in all directions from cell body	Spinal neurons Neurons of subcortical nuclei (e.g. inferior olive, pons, thalamus, striatum) Cerebellar granule cells
Partial 	Dendrites radiate from cell body in directions restricted to a part of a sphere	Neurons at edges of "closed" nuclei (e.g. Clarke's column, inferior olive, vestibular nuclei)
Laminar radiation		
Planar 	Dendrites radiate from cell body in all directions within a thin domain	Retinal horizontal cells
Offset 	Plane of radial dendrites offset from cell body by one or more stems	Retinal ganglion cells
Multi 	Cell has multiple layers of radial dendrites	Retinal amacrine cells

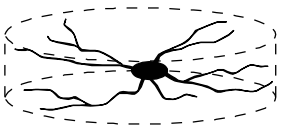
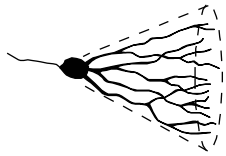
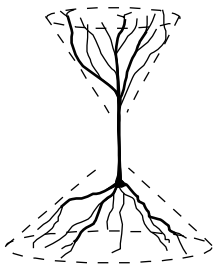
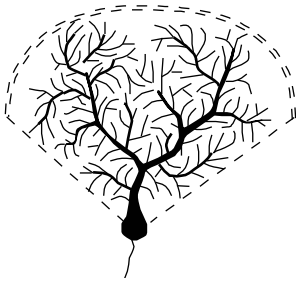
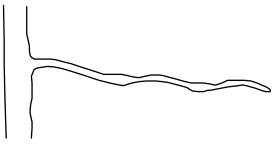
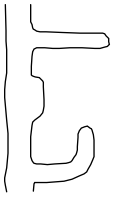
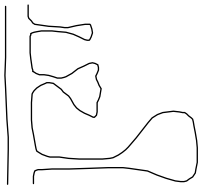
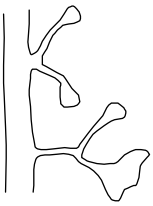
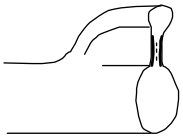
Cylindrical radiation 	Dendrites ramify from a central soma or dendrite in a thick cylindrical (disk-shaped) domain	Pallidal neurons Reticular neurons
Conical radiation 	Dendrites radiate from cell body or apical stem within a cone or paraboloid	Granule cells of dentate gyrus and olfactory bulb Primary dendrites of mitral cells of olfactory bulb Semilunar cells of piriform cortex
Biconical radiation 	Dendrites radiate in opposite directions from the cell body	Bitufted, double bouquet, and pyramidal cells of cerebral cortex Vertical cells of superior colliculus
Fan radiation 	One or a few dendrites radiate from cell body in a flat fan shape	Cerebellar Purkinje cells

Table 1.3 Synaptic specializations of dendrites

Pattern	Characteristics	Examples
Shaft 	Synapses occur directly on the surface of the dendritic shaft without obvious swelling or specialization	Interneurons
Varicosity 	An enlargement in a thinner dendrite associated with synaptic contacts	Retinal amacrine cells
Filopodium 	A long, thin protrusion with a dense actin matrix and few internal organelles	All neurons during developmental synaptogenesis
Simple Spine		
Sessile 	Synaptic protrusions without a neck constriction	
	Sessile spine	Cerebral pyramidal cells
	Stubby spine	Cerebral pyramidal cells
	Crook thorn	Neurons of dentate nucleus
Pedunculated 	Bulbous enlargement at tip	
	Thin spine	Cerebral pyramidal cells
	Mushroom spine	Cerebral pyramidal cells
	Gemmule	Olfactory bulb granule cell
Branched Spine 	Each branch has a unique presynaptic partner and each branch has the shape characteristics of a simple spine	CA1 pyramidal cells Granule cells of dentate gyrus Cerebellar Purkinje cells

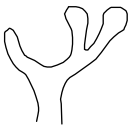
Synaptic Crest



Crest-like protrusion with a synapse on either side of a thin lamellar neck region

Cerebral pyramidal cells
Neurons of habenula, subfornical organ, and interpeduncular nucleus

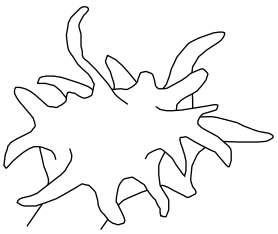
Claw Ending



Synaptic protrusions at the tip of the dendrite associated with one or more glomeruli

Granule cells of cerebellar cortex and dorsal cochlear nucleus

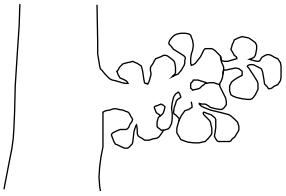
Brush Ending



Spray of complex dendritic protrusions at the end of dendrite that extends into glomerulus and contains presynaptic elements

Unipolar brush cells of cerebellar cortex and dorsal cochlear nucleus

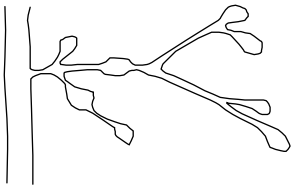
Thorny Excrescence



Densely lobed dendritic protrusion into a glomerulus

Proximal dendrites of CA3 pyramidal cells and dentate gyrus mossy cells
Proximal dendrites of thalamocortical relay cells

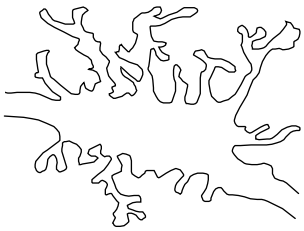
Racemose Appendage



Twig-like branched dendritic appendages that contain synaptic varicosities and bulbous tips

Inferior olivary neurons
Relay cells of lateral geniculate nucleus

Coralline Excrescence



Dendritic varicosity extending numerous thin protrusions, velamentous expansions and tendrils

Neurons of dentate nucleus and lateral vestibular nucleus

Table 1.4 Dimensions of simple spines on spiny neurons

Neuron	Neck diameter (μm)	Volume (μm^3)	Surface area (μm^2)	Synapse area (μm^2)	Ratio of synapse area to surface area
Cerebellar Purkinje cell	0.1-0.3	0.06-0.2	0.7-2	0.04-0.4	0.17±0.09
CA1 pyramidal cell	0.04-0.5	0.004-0.6	0.1-4	0.01-0.5	0.12±0.06
Visual cortex pyramidal cell	0.07-0.5	0.02-0.8	0.5-5	0.02-0.7	0.10±0.04
Neostriatal spiny neuron	0.1-0.3	0.04-0.3	0.6-3	0.02-0.3	0.125
Dentate gryus granule cell	0.05-0.5	0.003-0.2	0.1-3	0.003-0.2	—

Sources: Harris and Stevens (1988); Harris and Stevens (1989); Spacek and Hartman (1983); Wilson *et al.* (1983); Trommald and Hullenburg (1997)

Figure 1.1 – 2015 Dendrites Chapter 1 Harris and Spacek

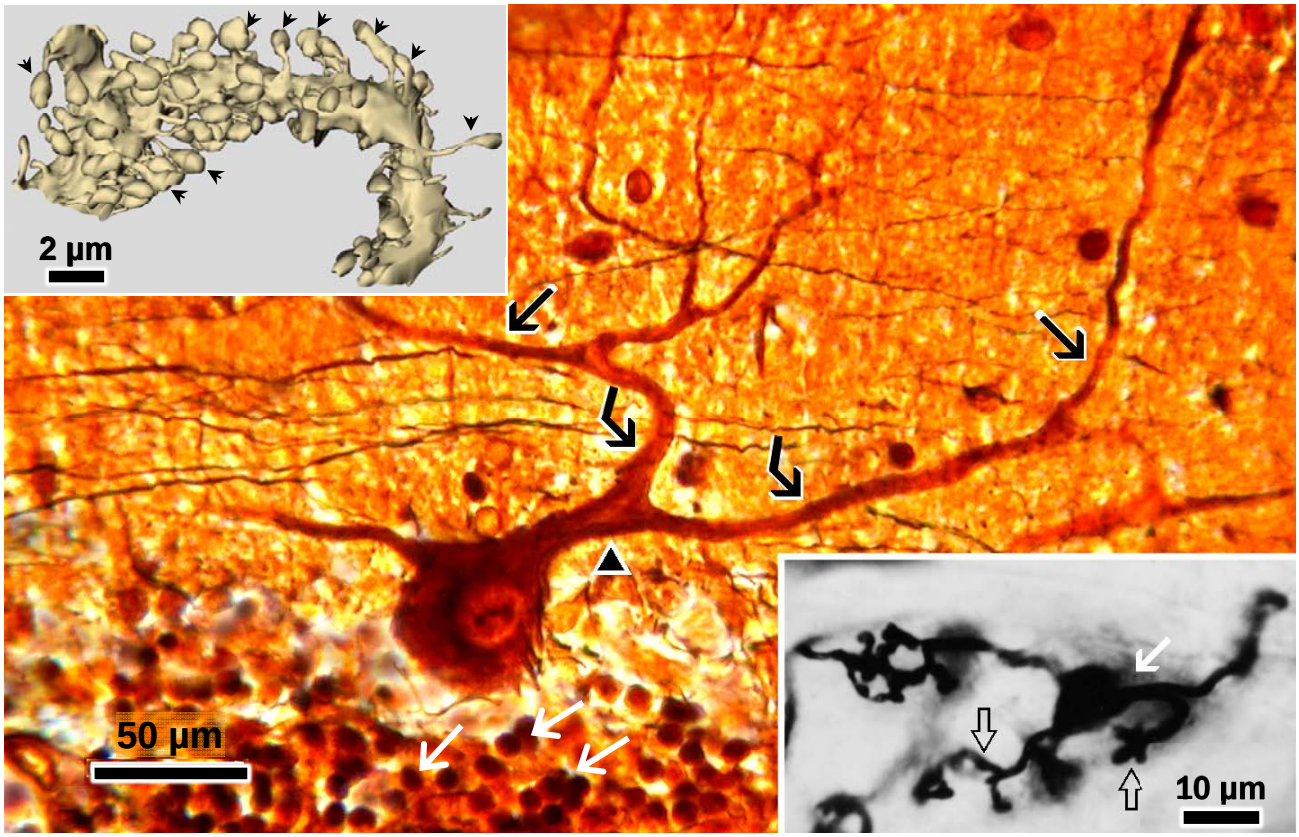


Figure 1.2 – 2015 Dendrites Chapter 1 Harris and Spacek

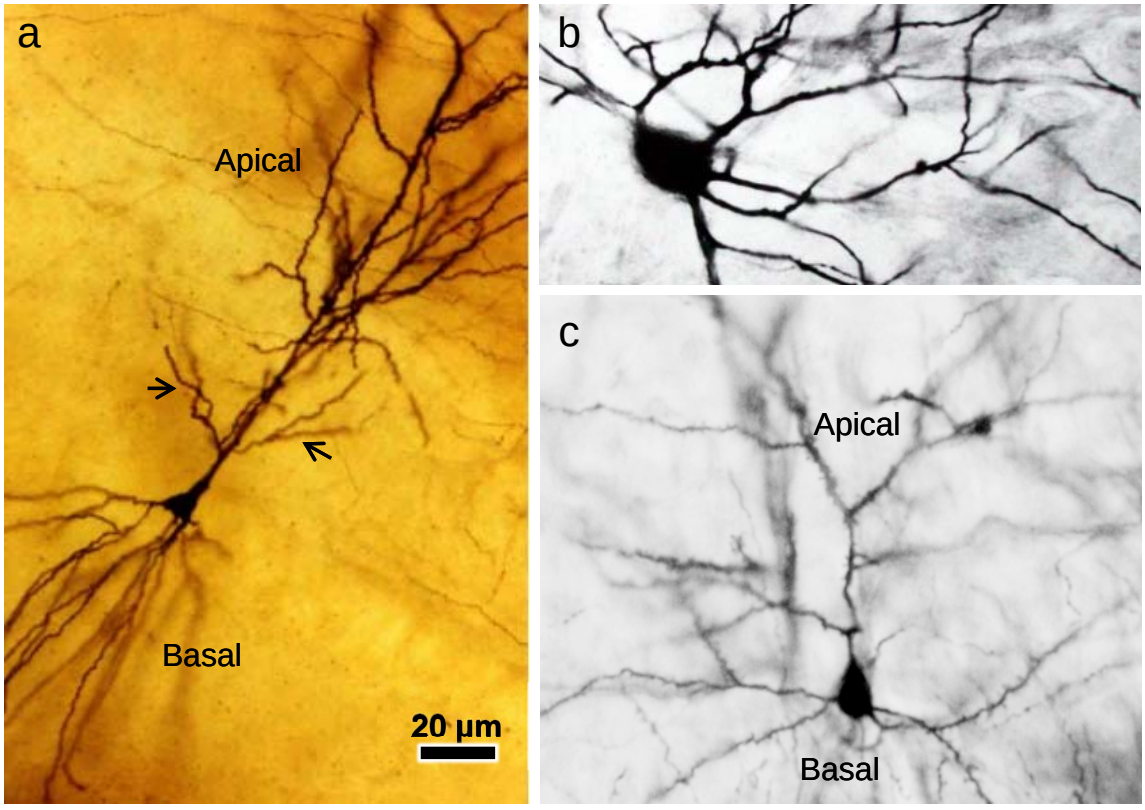


Figure 1.3 – 2015 Dendrites Chapter 1 Harris and Spacek

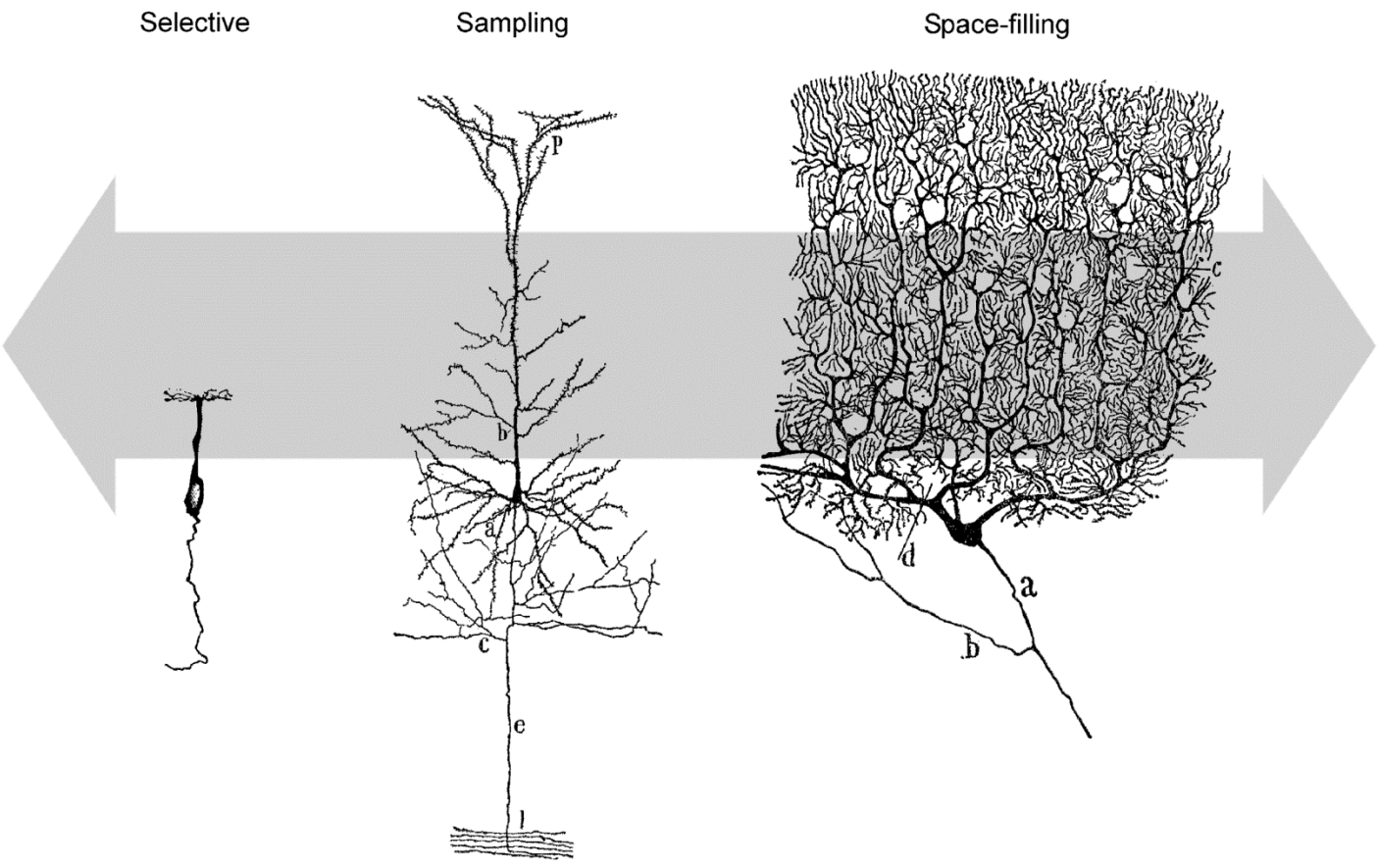


Figure 1.4 – 2015 Dendrites Chapter 1 Harris and Spacek

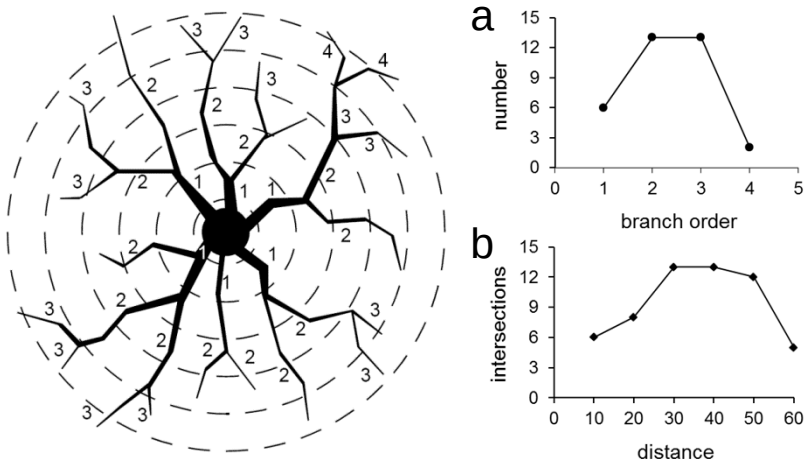


Figure 1.5 – 2015 Dendrites Chapter 1 Harris and Spacek
(Pictures without the cropped background)

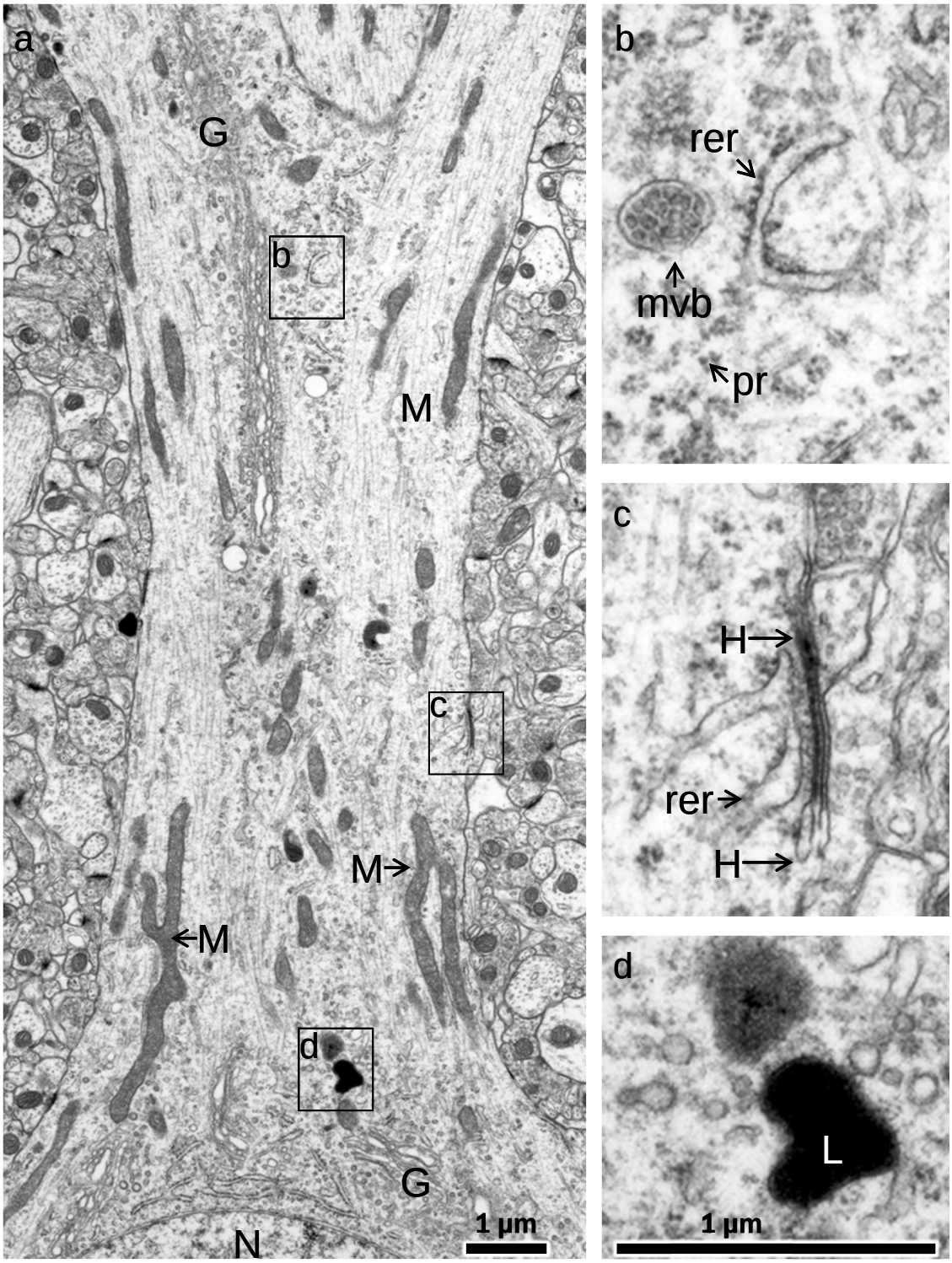


Figure 1.6 – 2015 Dendrites Chapter 1 Harris and Spacek

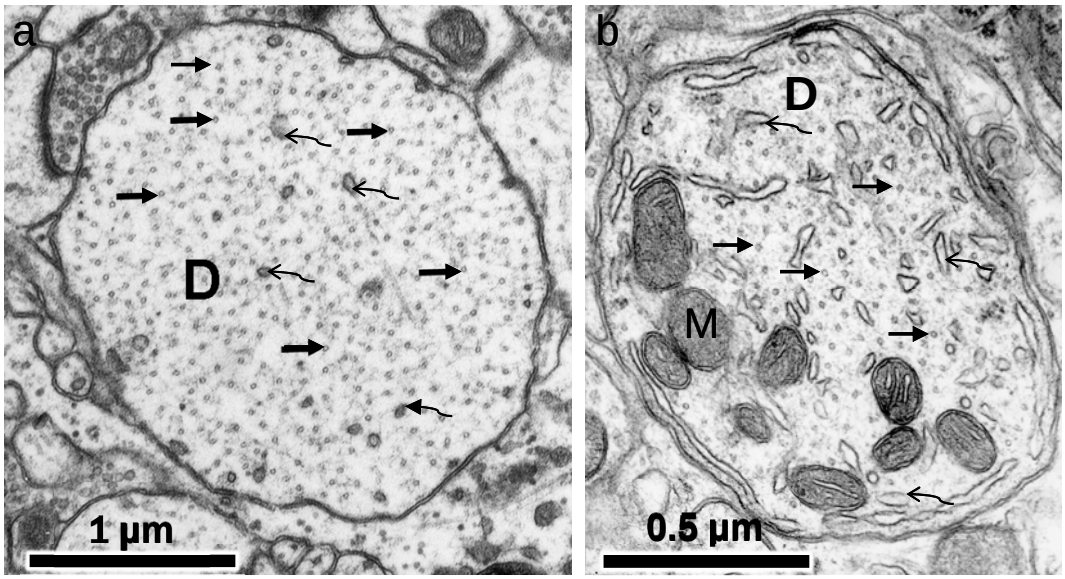


Figure 1.7 – 2015 Dendrites Chapter 1 Harris and Spacek

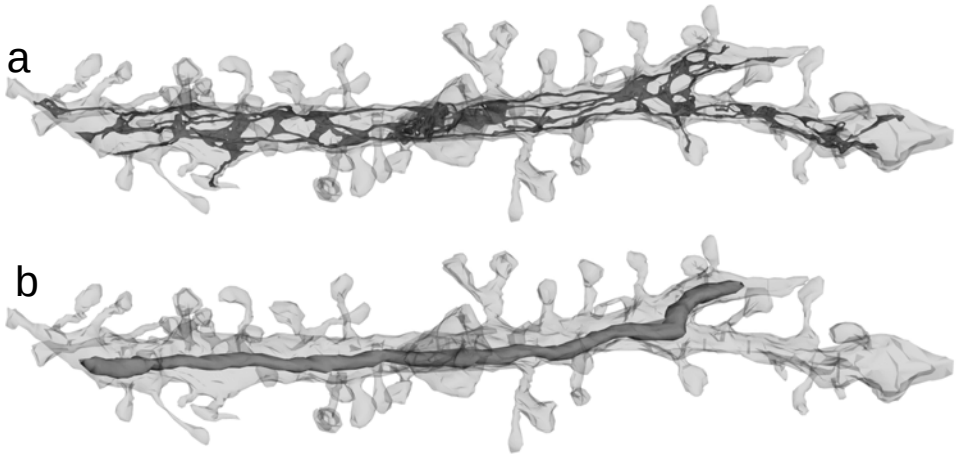


Figure 1.8 – 2015 Dendrites Chapter 1 Harris and Spacek

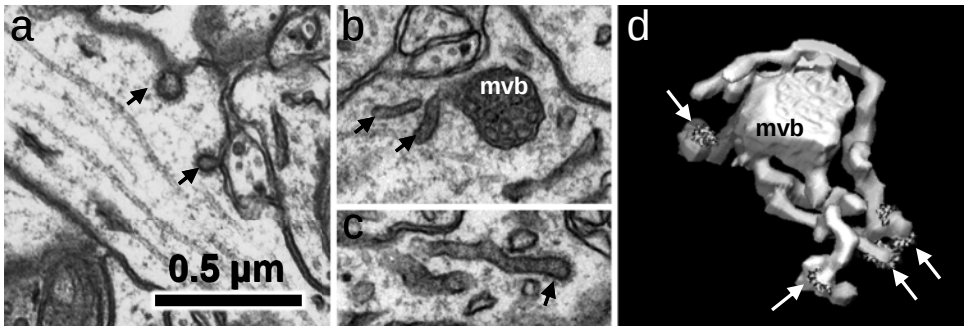


Figure 1.9 – 2015 Dendrites Chapter 1 Harris and Spacek

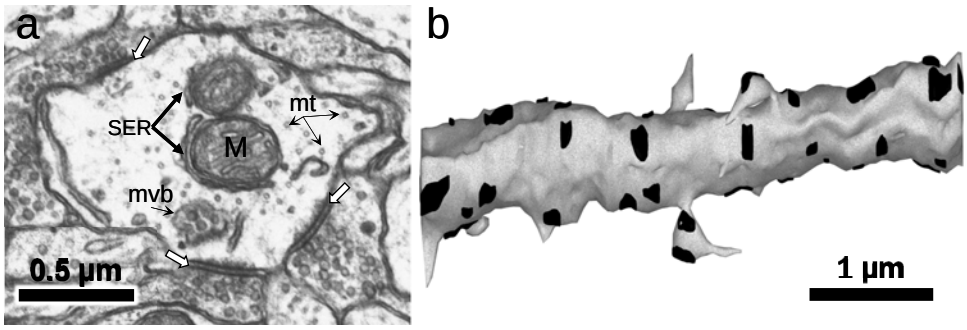


Figure 1.10 – 2015 Dendrites Chapter 1 Harris and Spacek

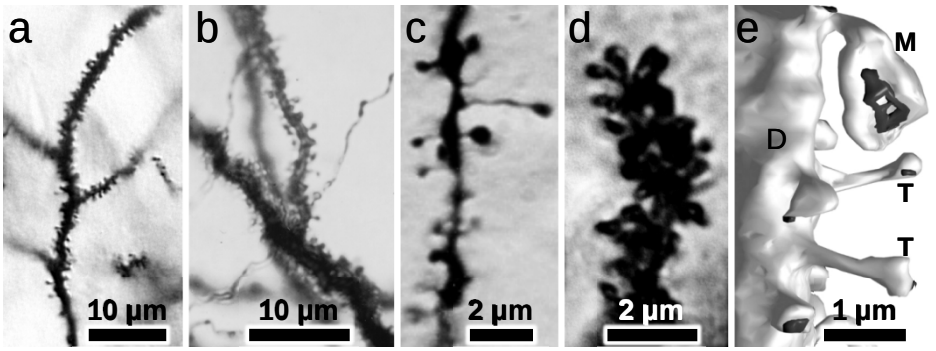


Figure 1.11 (former 1.14) – 2015 Dendrites Chapter 1 Harris and Spacek

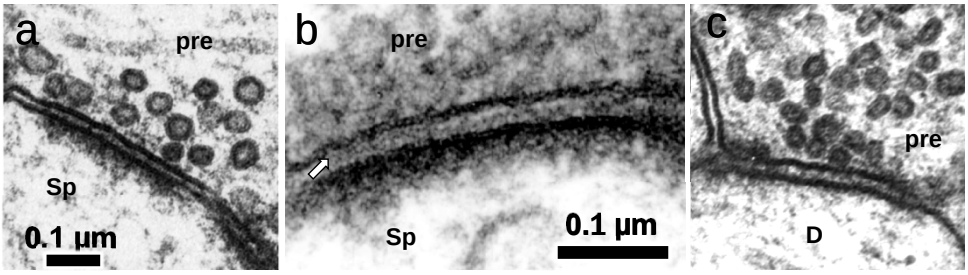


Figure 1.12 – 2015 Dendrites Chapter 1 Harris and Spacek

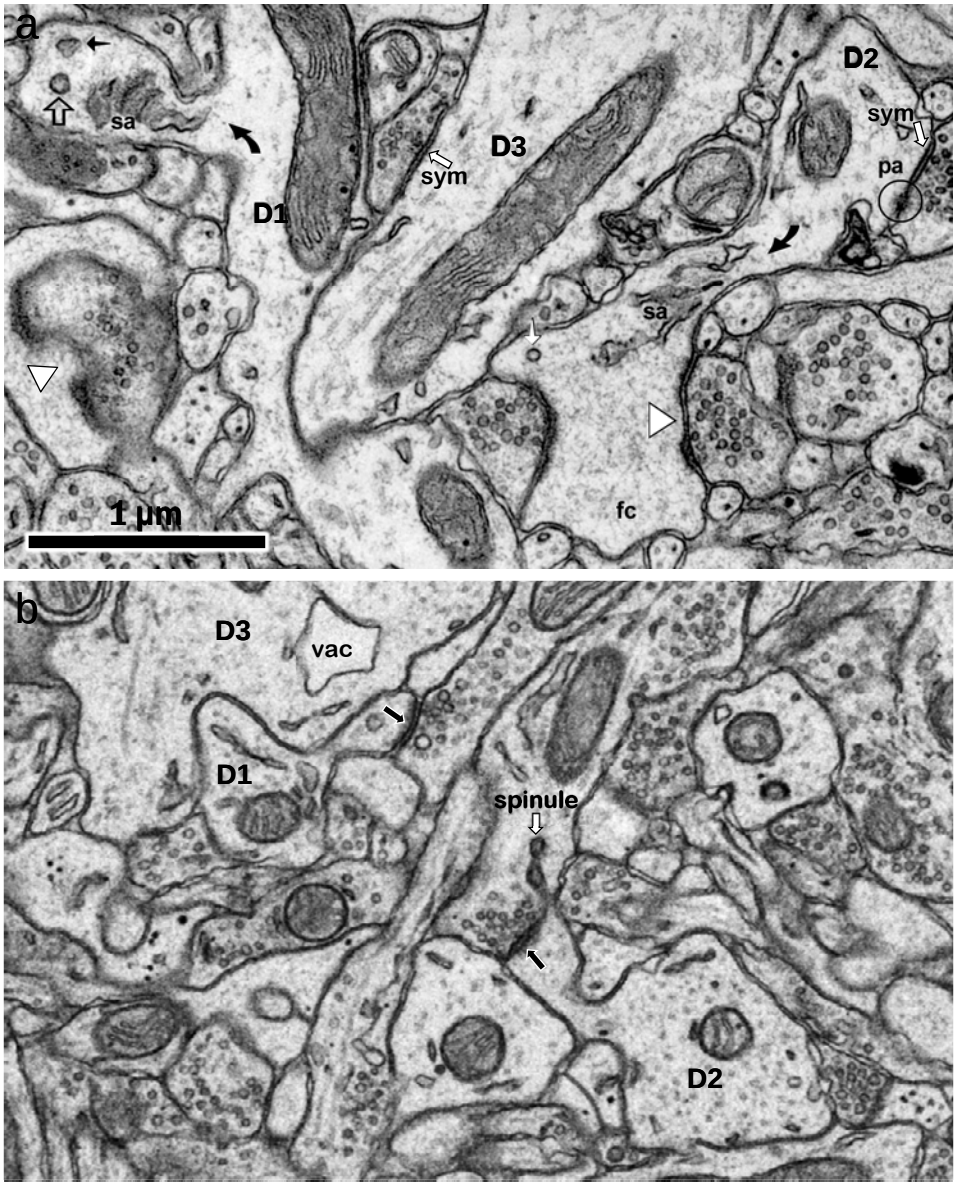


Figure 1.13 – 2015 Dendrites Chapter 1 Harris and Spacek

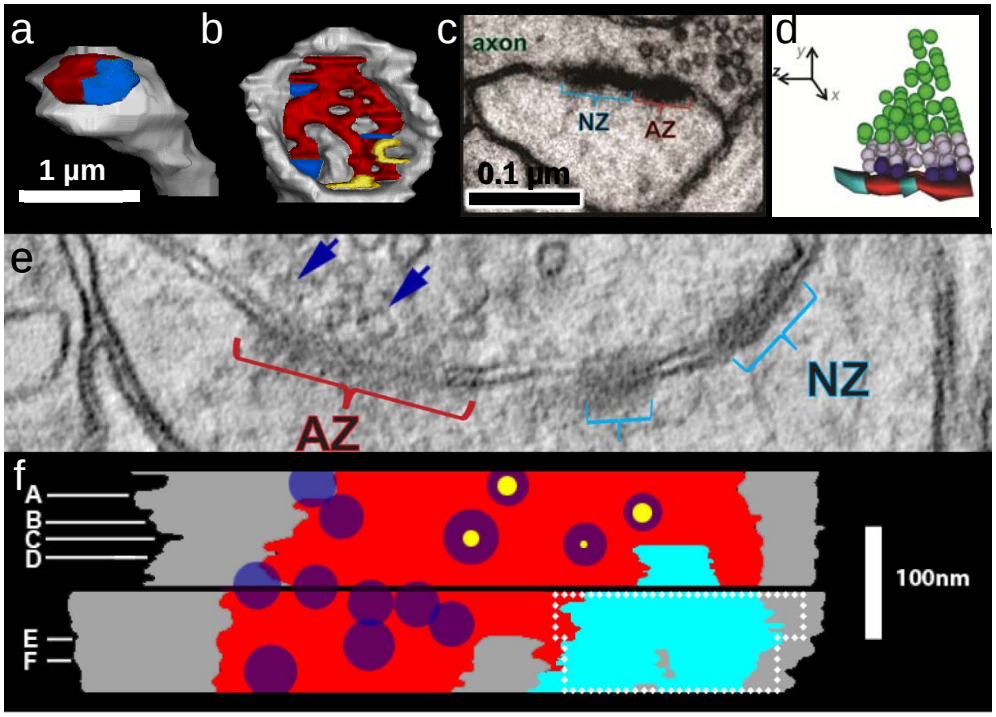


Figure 1.14– 2015 Dendrites Chapter 1 Harris and Spacek

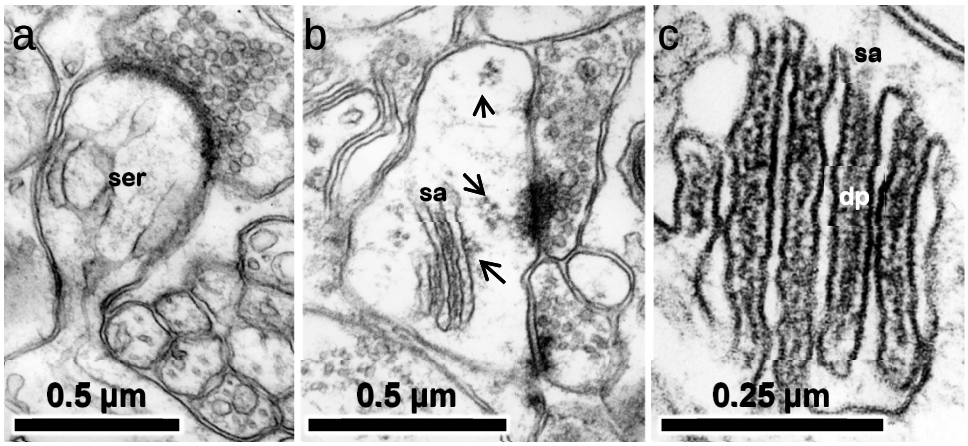


Figure 1.15– 2015 Dendrites Chapter 1 Harris and Spacek

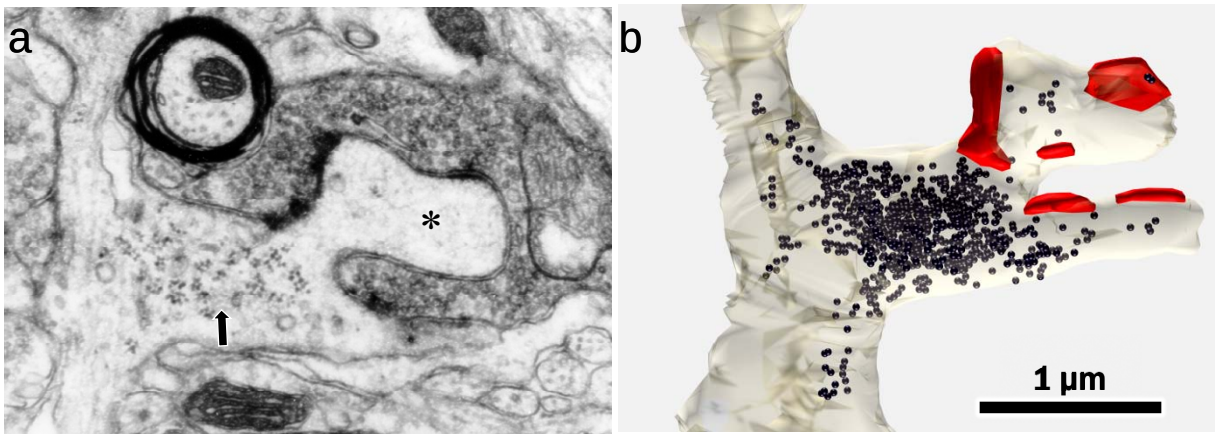


Figure 1.16 – 2015 Dendrites Chapter 1 Harris and Spacek