Chapter 2

Evolution and scaling of dendrites

Gayle M. Wittenberg, Samuel S.-H. Wang

Summary

Dendrites, the neuronal processes that receive synaptic inputs, are found in all nervous systems. The great diversity of dendrites, both within individual species and across phylogeny, reflects their adaptation to particular functional roles. In the present chapter we use this diversity to consider dendrites from an evolutionary perspective. We first describe some principles seen in the diversity of dendritic forms. We then seek to explain this diversity in terms of tradeoffs among functional optimization constraints; mechanistic limits set by the available molecular toolkit; and developmental mechanisms, the targets upon which selection has acted. Finally, based on these perspectives, we identify areas ripe for future investigation.

Introduction

Dendrites arising from various neurons share basic features at the level of molecules, cell biology, and biophysics. Yet they also show a remarkable diversity in form, molecular composition, integrative properties, and the ability to conduct action potentials. This diversity, which is found both among neuron types and in the same type of neuron across species, suggests the possibility that dendrites have adapted evolutionarily to fill a wide range of functional roles.

Although evolutionary changes in dendrites have not been observed directly, inferences about their history and relatedness can be made by comparative studies of living animals. Neurons in different species or brain regions may have similar evolutionary origins (homology) or play similar functional roles (analogy). Evidence for such similarities can be found by examining (a) structure or composition, (b) position in neural circuitry, (c) developmental history, (d) information-processing capabilities, and (e) functional role in a neural system.

Dendrite evolution must be considered in terms of the function of the entire system, the level at which selection directly occurs. Thus, dendrites may change as a direct result of selection pressure to optimize a specific function subject to constraints at the cellular or network level, as a byproduct of optimizing a different function, or simply as a result of genetic drift. We will review dendrite evolution in terms of observed variation in morphology, biophysics, and molecular composition. We describe possible evolutionary constraints influencing dendrites, including biophysical, energetic, and metabolic constraints, and the functional needs of the organism. Finally, we discuss how this diversity

may have arisen, considering not only genetic events, but also the role of developmental programs and homeostatic mechanisms on shaping the form and function of dendrites. Overall, this framework provides a means for understanding how and why dendrites vary.

Comparative anatomy: scaling of dendritic arbors with brain size

Broadly, neurons can be categorized according to whether or not they increase in complexity in animals with larger brains or bodies. This fundamental observation was first framed by Santiago Ramón y Cajal in 1911: 'From the appearance of the very first vertebrates, some individual neurons or groups of neurons have been modified more or less continuously before reaching their current state of refinement. In contrast, some neurons remain unchanged over long periods of time, seemingly impervious to all progress' (Ramón y Cajal 1995, p. 87).

After more than 100 years of comparative studies, Cajal's original factual observation of diversity remains intact. However, greater structural complexity is found in neurons from large brains in general, and not just 'refined' ones. Thus, dendritic size and structural complexity scale predominantly not with advancedness of the brain, but rather with absolute brain (and body) size (Purves 1988). This implies that dendritic form may be shaped largely by global tradeoffs common to all animals of a class.

The nervous system is special in this regard. Most organs scale with body size (Huxley 1932) by using cells that are of roughly the same size across species, but increasing the number of cells (Thompson 1942). The relative invariance of cell size across species is typical of a wide variety of cell types that continue to divide and therefore are renewed throughout life (Savage *et al.* 2007). Nonscaling cell types include liver cells, thyroid epithelial cells, renal epithelial cells, pancreatic acinar cells, and red blood cells (Levi 1905; Teissier 1939; Altman and Dittmer 1961; Purves 1988). With invariant cell size many cellular functions would be expected to scale up directly with cell number; for instance, doubling the number of red blood cells would double the amount of oxygen carried. In the case of neurons, the brain constitutes an interconnected network, and its information-processing capabilities depend not only on the number of neural elements, but also on the connections formed by it. The fact that most neurons and their dendrites become larger and more complex as overall brain or body size increases suggests that convergence (the number of synapses received by a neuron) and divergence (the number of neurons contacted by a neuron), which contribute integrally to the overall information-processing capability of the brain are single-cell properties that scale positively with overall network size. Changes in convergence are reflected at least to some degree by the overall size of the dendrite. Understanding the principles governing which types of dendrites do not scale with brain size, and which dendrites do scale, may aid in understanding their different roles in information processing (Figure 2.1).

Neurons that stay the same

Some types of neurons vary relatively little in size or structural complexity among vertebrates. In these cases the dominant optimization principle may occur at a single-cell

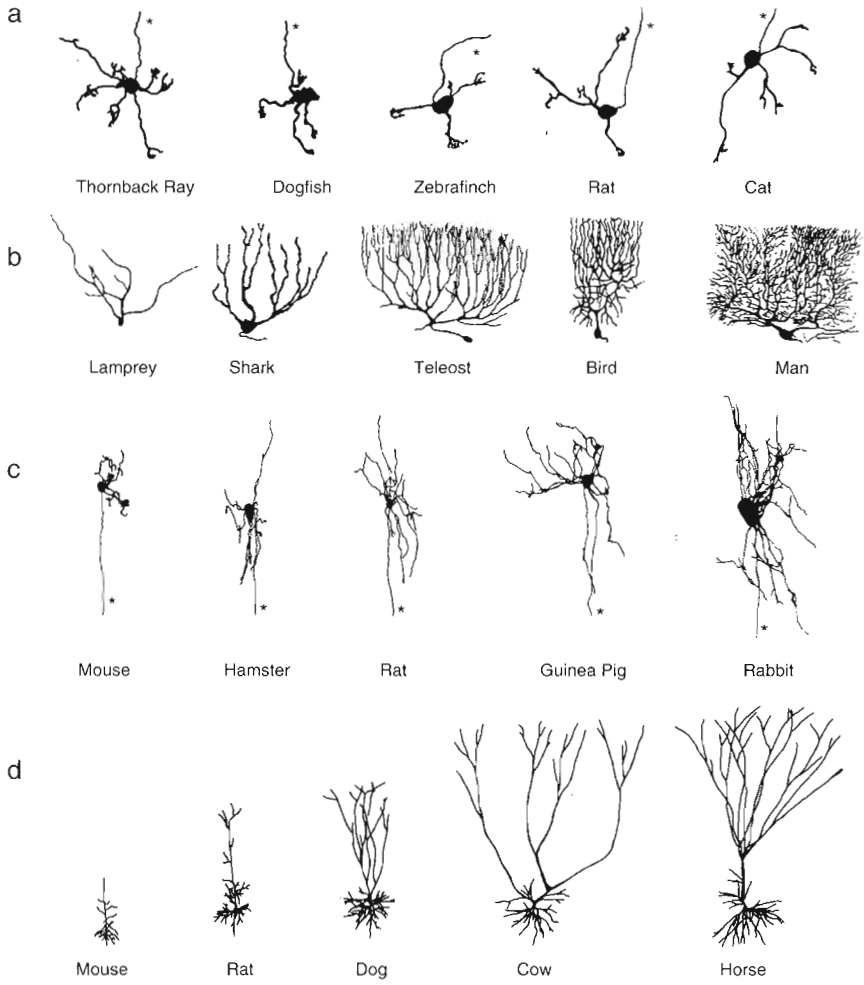

Fig. 2.1 Comparison of vertebrate dendrites across phylogeny. **(a)** Cerebellar granule cells. Thornback ray from Nicholson *et al.* 1969; dogfish from Schaper 1898; zebra finch, rat, and cat from our own laboratory. **(b)** Cerebellar Purkinje neurons (Nieuwenhuys 1967). Neurons in panels a and b are scaled to fit page. **(c)** Sympathetic neurons (Purves 1988). **(d)** Neocortical pyramidal neurons (Purves 1988, from Barasa 1960). Neurons in panels c and d are scaled to reflect their true size relative to one another. Where appropriate, axons are indicated with asterisks (*)

level, such as a requirement for a fixed number of synaptic inputs or for temporal precision.

A prominent example of neuronal constancy is the cerebellar granule cell. Granule cells are a canonical element of the cerebellum, a major division of nearly all vertebrate brains (Eccles 1969; Llinás 1969; Nieuwenhuys *et al.* 1998), (Figure 2.1a). Cerebellar granule cells have a small cell diameter and extrude four or five short, clawed dendrites, which receive input from mossy fibers (Palay and Chan-Palay 1974). This overall structure is

found universally in all cerebella, including that of one of the most primitive vertebrates, the dogfish (Alvarez and Anadon 1987). The most salient change in cerebellar granule cell evolution is the appearance of a T-junction in the granule cell axon to form two axonal branches per parallel fiber. The constancy of dendritic structure suggests that the number of mossy fiber inputs per granule cell is central to its role in information processing. This constancy of granule cell structure contrasts with the fact that their main postsynaptic targets, Purkinje cell dendrites, vary considerably across phylogeny, (Figure 2.1b). This scaling of Purkinje cell dendrites may be developmentally driven by the amount of trophic support provided by increasing numbers of granule cells in larger brains, a topic to which we will return.

Receptor cells are in many cases also unchanging across species. For instance, in the retina, rod outer segments from diurnal mammals are of fairly uniform length and diameter (Sterling 2003), and these dimensions are similar in other warm-blooded animals such as nocturnal mammals (Sterling 2003) and birds (Braekevelt 1998; Rojas *et al.* 2004). Rods in these animals are uniformly narrow, 1–2 μm in diameter, ensuring a rapid response time and concomitant with the fact that mammals and birds move quickly. Temporal performance requirements may thus impose a general cell-level constraint across species (Sterling 2003). In contrast, some cold-blooded vertebrates that move more slowly have considerably larger rods (for instance, fivefold wider in sluggish amphibians) with correspondingly slower response times (Sterling 1997). Thus, optimization of rod structure appears to respond to organismal selection expressed directly on single-cell functional properties, without regard to network size.

Neurons that change as brains get larger

In contrast to granule cells, most other neuronal types vary in their dendritic complexity across species (Figure 2.1b,c,d). In these cases the general form of the dendrite remains recognizable across species, although the addition and loss of dendritic elements can occur (Dryer and Graziadei 1994). Typically, cell body diameter and dendritic arbor size both increase as a function of body size (and therefore of brain size) (Bok 1959; Purves and Lichtman 1985; Snider 1987; Kötter and Feizelmeier 1998). Scaling of dendritic s ize occurs throughout the peripheral and central nervous system. Examples include sympathetic ganglion cells (Ebbesson 1968a, 1968b; Purves and Lichtman 1985), olfactory mitral cells (Dryer and Graziadei 1994), thalamocortical neurons (Ohara and Havton 1994), cerebellar Purkinje neurons (Smolyaninov 1971; Harvey and Napper 1991), substantia nigra neurons (Yelnik *et al.* 1987; Tepper *et al.* 1994; Kötter and Feizelmeier 1998), hippocampal mossy cells (Buckmaster and Amaral 2001), and pyramidal neurons of the hippocampus (Bekkers and Stevens 1990; Buckmaster and Amaral, 2001), entorhinal cortex (Buckmaster *et al.* 2004), and neocortex (Barasa 1960; Ramón y Cajal 1995; Elston *et al.* 2001).

Although dendrites are often larger and more branching in large animals, their general forms are preserved across species. In somatosensory thalamocortical projection neurons, Ohara and Havton (1994) found in rat, cat, and macaque that total dendritic length per neuron varied, but branching parameters such as degree of bifurcation and terminal branch order were conserved. Similar conservation of dendritic branching form

has been found among several neuron types of the substantia nigra in rat, macaque, and human (Yelnik *et al.* 1987; Tepper *et al.* 1994; Kötter and Feizelmeier 1998) and in frog, rat, and cat motoneurons (Dityatev *et al.* 2001). This conservation of branch patterning suggests that dendrites grow according to shared developmental mechanisms.

A case study: sympathetic neurons

A particularly well-studied case of dendritic diversity is that of autonomic ganglion cells (Figure 2.1c). These neurons are unusual in that they have only one axonal input per dendrite. Scaling principles in these neurons have been investigated extensively (Ebbesson 1968a; 1968b; Forehand 1985; Purves and Lichtman 1985; Purves *et al.* 1986; Snider 1987; Ivanov and Purves 1989).

Purves and colleagues made a number of correlative measurements in five mammals ranging in body size (and target size, in this case the eyeball) from mouse to rabbit. They found that the number of sympathetic neurons increased with body size, but did not maintain proportionality. However, they also found that sympathetic neurons from larger-sized animals have more dendrites (Purves and Lichtman 1985) and larger cell bodies (Snider 1987). Increases in dendrite number are matched one-to-one by increases in the number of innervating axons: a neuron with no dendrites or one dendrite typically has one input, one with two dendrites two inputs, and so on (Lichtman and Purves 1980; Lichtman *et al.* 1980; Purves and Hume 1981; Hume and Purves 1983; Forehand 1985; Purves and Lichtman 1985).

They suggested that in the sympathetic periphery, the number of dendrites, by modulating competition among the axons innervating the same neuron, determines the number of inputs. Thus, cell number and dendritic complexity may both provide ways to match target size with the total amount of central drive (Purves 1988). The fact that scaling occurs at these different stages of processing suggests that adaptations that match a neural system to target size can be distributed over multiple steps of the neural pathway.

Comparative anatomy: scaling and biophysics of dendrite diameter

Dendrites vary not only in form but also in diameter along their length. Variations in dendritic diameter are important determinants of both electrical signaling properties and transport properties (Hillman 1979). These functions may therefore play a critical role in optimizing the shape of dendrites.

As dendrites become larger and more branched, voltage signals traverse a longer distance before reaching the cell body and therefore may be affected more by the filtering properties of the dendritic membrane. These properties are determined by the diameter of the dendrite. In wider dendrites, passive signals are attenuated less, and both passive spread and active propagation are faster (Rall 1977). Because of this relationship between diameter and signaling properties, the form of a dendrite might be shaped in part by its signal integration requirements (Purves and Lichtman 1985; Bekkers and Stevens 1990; Olsen *et al.* 1996).

Indeed, dendrites do show great variability in diameter scaling. At one extreme is no scaling, in which dendrites are of similar diameter regardless of length. This trend would be sufficient to support signaling in short dendrites, where passive losses are minimal; or in active dendrites, assuming negligible conduction delays. At the other extreme are dendrites whose thickness increases as the square of total dendrite length. This scaling would tend to conserve the amount of passive attenuation along the length of the dendrite. These forms of dendritic scaling, as well as intermediate cases, have been observed across species and are discussed below. The type of scaling that occurs plays a key role in the properties of signal integration by the dendrite as a whole.

Non-scaling dendrites

Non-scaling (constant diameter across species) dendrites have been observed in neurons of the pars reticulata and pars lateralis of the substantia nigra (Yelnik *et al.* 1987; reviewed by Kötter and Feizelmeier 1998). In these neurons, soma diameter and dendritic length are larger in humans than in macaques, but dendrite thickness is about the same. Such a lack of scaling suggests that in these neurons, input location does not influence integration by postsynaptic summation mechanisms (Bekkers and Stevens 1990). This would occur if, for instance, information processing in these neurons were dominated by regenerative events in dendrites or the cell body.

Constant-diameter dendrites would also be expected in neurons that receive input from only one axon per dendrite, such as cerebellar granule cells. In these neurons, summation occurs at the cell body, and a single input may be sufficient to cause the cell to fire. In this situation small dendrites might be favored as a means of reducing capacitance and therefore the energy cost of changes in membrane voltage. This comparative measurement has not been done (though note the apparent similarity of traced dendritic thickness across species in another cell type with one input per dendrite, superior cervical ganglion cells (Purves and Lichtman 1985)).

Another case in which dendritic diameter is approximately constant is hippocampal dentate gyrus granule cells (Bekkers and Stevens 1990). In a comparison of human and cat, principal dendritic shafts measured at the midpoint of the arbor were of similar diameter. More detailed measurements in macaque and rat show that dentate gyrus granule cells (St. John *et al.* 1997) have similar total dendritic length, somatic area, and passive electrical properties, but somewhat different action potential widths. A modest increase in the vertical extent of dendrites occurs in larger animals (St. John *et al.* 1997).

Isoelectrotonic scaling

At the other extreme of scaling, Bekkers and Stevens reported that dendrites might vary in an electrotonically conservative fashion across species (cat versus human) in the apical dendritic shafts of CA1 pyramidal neurons. These main shafts were substantially thicker in human than in cat. They proposed that dendritic diameter scaled up as the square of dendrite length in order to preserve the electrotonic distance from the cell body to the ends of the dendrites. This would be consistent with a more passive summation process in apical dendrites. Thickening of dendrites also argues against active processes, since

active amplification in a thicker process would add to the energy cost without contributing to signal integration properties.

The measurements of Bekkers and Stevens were made at a single site halfway up the apical dendrite. However, the scaling of apical dendrites would not necessarily be true of basal dendrites, which in rat can generate local regenerative voltage events (Polsky *et al.* 2004). Even within the apical dendrite, regenerative spike-like events can be induced in distal dendrites (Golding *et al.* 2002) and plateau potentials can be induced in both distal and oblique dendrites (Cai *et al.*, 2004). Dendritic action potentials may serve multiple functions, including the propagation of signals to guide associative plasticity (Hebb 1949; Brown *et al.* 1988; Raymond *et al.* 1996; Malenka and Nicoll 1999), reset excitability (Hausser *et al.* 2001), and even drive secretory events (Lledo *et al.* 1998). These possibilities suggest the need for measurements of dendritic diameter at multiple sites, and correlation with physiological observations.

Scaling of dendrite diameter with length has also been studied over the lifetime of an individual as it grows. Isoelectrotonic growth has been observed in the medial giant interneuron of the cricket, in which passive membrane integrative properties are preserved even as the organism increases sevenfold in length and the dendrite increases 2.6-fold in length (Hill *et al.* 1994). Isoelectrotonic scaling is also observed in some retinal ganglion cells in the rainbow trout (Picones *et al.* 2003). In both of these examples, the relative efficacies of synapses on different locations of the arbor are preserved independently of the size or pattern of their dendritic arbor.

Intermediate scaling

Intermediate cases of scaling of dendritic diameter have also been observed. In type I neurons of the substantia nigra pars compacta, the maximal dendrite length is progressively larger from rat to macaque to human (Yelnik *et al.* 1987; Tepper *et al.* 1994; Kötter and Feizelmeier 1998). However, diameters scale up only linearly (isometrically) with dendrite length, insufficient to preserve electrotonic properties (Kötter and Feizelmeier 1998). In these cases conservation of electrotonic function would require additional scaling of channel density and the balance and distribution of channels (Kötter and Feizelmeier 1998). Isometric scaling of dendrites has also been observed during growth of the lateral giant interneuron of crayfish (Edwards *et al.* 1994; Hill *et al.* 1994) and in some retinal ganglion cells in the rainbow trout (Picones *et al.* 2003). Isometric scaling may represent a case in which the exact integrative properties of dendrites are not critical to the neuron's function.

Other biophysical constraints

Preservation of electrotonic properties is not the only possible explanation for the scaling of dendritic diameters. Dendrites are also conduits for the transport of materials along their length. As a result, they may need to move material efficiently. Evidence for this comes from the observation that when a dendrite branches, the daughter branches are smaller in diameter than the parent branch (Lux *et al.* 1970; Barrett and Crill 1974a; 1974b; Hillman 1979). Daughter branches d_1, d_2, and the parent diameter D approximately observe the relationship $d_1^N + d_2^N = D^N$, where N ranges from 1.5 to 2. An exponent of

N=2 indicates preservation of cross-sectional area before and after a branch point, a condition that would preserve per-area rates of transport; this has been seen in pyramidal and Purkinje cells (Hillman 1979). An exponent of N=1.5 is consistent with preservation of charge and has been approximately observed in motoneurons (Lux *et al.* 1970; Barrett and Crill 1974a; 1974b; Hillman 1979). In any case, this range of exponents corresponds to a fairly narrow range of branching ratios; for symmetric bifurcations, exponents between 1.5 and 2 correspond to a daughter branch being 0.63–0.71 times as wide as its parent, making possibilities within this range hard to distinguish anatomically.

This branching may contribute to observations of diameter scaling. If in CA1 pyramidal neurons the branching depth (number of branch points between soma and dendritic tips) depends on the arbor diameter and the terminal tip diameter is constant, then the diameter at the midpoint of the arbor would have to be larger in human pyramidal neurons, which are more elaborate and have more branches than their counterparts in smaller-brained mammals.

Thus, dendritic diameter scales in two ways: (a) across species, at a defined location, diameter is either constant or scales up as a function of arbor size; (b) within an individual arbor, with successive branching, diameter decreases. Taken together, these phenomena suggest that scaling of dendrite diameter is related to dendrite-specific mechanisms for establishing a branched architecture. If the size of the smallest dendritic structures is conserved, variations in diameter may regulate the total size of the arbor and thus the degree of synaptic convergence (Purves 1988; Chklovskii 2000). Dendrite diameter also affects cable and electrical signaling properties (Purves 1988; Bekkers and Stevens 1990) and may be optimized for efficient transport of materials (West *et al.* 1997; Banavar *et al.* 1999). The fact that a dendrite must carry out all of these functions suggests that scaling of dendritic diameter may result from the competing influence of these needs.

A constant underlying unit: the single synapse?

Even when dendrites vary, their components might still remain constant if function is optimized locally. Examples of local function include chemical signals such as synaptic transmission and second messenger signaling, and cell biological phenomena such as vesicle trafficking and secretion. One neuronal structure at which all of these functions occur is the synapse. In the mammalian neocortex, the total density of synapses per unit volume is remarkably constant among both functional areas and species (Schüz and Demianenko 1995; reviewed in Harrison *et al.* 2002). Thus, on average, the amount of volume available to a bouton-plus-spine may be relatively constant across species. This raises the possibility of *synaptic constancy*: single presynaptic and postsynaptic terminals of a given type may be similar in size across species, and be optimized in a way that is independent of overall brain size. This question has not been fully investigated.

Comparative physiology: expression patterns of dendritic molecules

In addition to physical form, another feature distinguishing dendrites of different neuronal types is the expression pattern of various molecules important for dendrite function.

In vertebrates, reception and processing of signals on dendrites begins primarily at chemical synapses. The subsequent processing of inputs is determined by both the composition and the spatial distribution of passive and active ion channels in the arbor and the complement of neurotransmitters, neuromodulators, postsynaptic receptors, and signal transduction machinery. The manner in which neuronal inputs are processed can change over time through synaptic plasticity, which depends on many signaling molecules, including the NMDA receptor, metabotropic glutamate receptors, IP_3 and ryanodine receptors, calcium buffer proteins, and downstream kinases and phosphatases.

These molecular building blocks are found across the vertebrates, and some in a wider variety of organisms. However, even among neurons their expression can vary considerably. For example, excitatory pyramidal neurons of neocortical areas and the hippocampus have apical dendrites in which action potentials can backpropagate at least partway, which when paired with presynaptic activation can induce synaptic plasticity (Magee and Johnston 1997; Markram *et al.* 1997). The large tree-like Purkinje cell dendrites, on the other hand, do not support action potential backpropagation at all, but instead generate calcium channel-based action potentials (Llinás and Sugimori 1980). However, like pyramidal neuron action potentials, these calcium-based action potentials can also drive synaptic plasticity (Raymond *et al.* 1996). Neurons also differ greatly in their firing properties. These properties are set in part by patterns of channel expression on the soma and dendritic arbor. Additional differences exist at the level of cell biology, neurochemistry, receptor type, and plasticity transduction machinery. This great diversity suggests that different cell types have evolved either to perform different computations or under different sets of constraints. Contrasts of dendrites among neuron classes are discussed in detail elsewhere in this text (see Chapters 1, 7, 8, and 9).

Unfortunately, these differences are all studied principally within single species, usually rats; comparative molecular and physiological information from multiple species is scarce. Although it is true that in recent years a large body of comparative DNA and protein sequence information has accumulated, functional comparative information, for instance about channel kinetics and distribution, firing properties, or signaling properties, has not been gathered. This is a major area of ignorance in the study of the evolution of dendrites, and of neurons in general.

A handful of studies illustrate the potential of comparative studies to yield insights into neuronal function. In the cerebellum, Llinás and coworkers have found that the climbing fiber input triggers a characteristic, dendritically generated complex spike that takes on a similar multiphasic waveform in the Purkinje neurons of mammals, alligator, frog, and an elasmobranch fish (Llinás 1969). These spikes have been suggested to provide an instructive signal to guide plasticity (Raymond *et al.* 1996) and to control pauses in simple spiking (Bloedel and Bracha 1998); whatever their function, their role is likely to be as old as the vertebrates. In an example of dissimilarity across species, resting firing rates of sympathetic neurons increase with body size (Ivanov and Purves 1989); both subthreshold and suprathreshold activity rates are higher in larger mammals. This variation may be driven by progressively larger amounts of converging synaptic drive, in line with anatomical findings (see 'Comparative anatomy' above), and provide an example in which firing

rates are not conserved across phylogeny. Finally, at the level of channels, gating parameters may be adapted across species. In a variety of mollusks, sodium channel gating parameters are correlated with locomotory speed (Gilly *et al.* 1997); animals with faster rates of movement have faster neuronal sodium channel gating.

Network-level constraints influencing dendritic form

While several clear trends are seen in how dendrites scale with brain or body size, clear statements as to *why* any trend is seen at the dendritic level are difficult to make with any certainty. The fitness of a neural phenotype is likely to reflect a combination of information-processing needs in single dendrites, network-level functional requirements, and global energetic constraints. Along these lines a number of functional principles have been suggested.

Metabolic/energetic cost and wire length minimization

Neural tissue is energetically costly to operate; this creates pressure to minimize metabolic energy costs from neuronal activity (Attwell and Laughlin 2001). As a result, developmental mechanisms would be expected to drive dendrites to take forms that minimize volume and/or length (Cherniak 1994; Van Essen 1997; Chklovskii and Stevens 2000; Zhang and Sejnowski 2000; Changizi 2001). For instance, in layered structures a particular width of dendritic arbor can minimize and equalize the total volumes of axons and dendrites; the arbor width may therefore be closely related to synaptic convergence and divergence ratios (Chklovskii 2000), and the branching patterns of arbors may have the smallest possible length to achieve a given interconnectivity (Chklovskii 2004).

Input convergence and network architecture

Central neurons may also be constrained by the need to communicate with one another within the brain. This may drive the need for dendritic arbors to receive input from more neurons. This is subject to constraints of the connectivity that is possible within a large network. For instance, connecting to a constant fraction of the neurons within a neural structure cannot be scaled up because the total number of synaptic elements would then need to scale up as the square of the number of neurons. This would lead to runaway increases in volume (Ringo 1991; Changizi 2001). However, a functional network architecture may not require the number of synapses per dendritic arbor to scale proportionally with brain size. Instead, in a recurrently connected network a parameter of great functional interest is the network diameter, defined as the minimum number of synapses connecting any two neurons, on average. Maintaining the network diameter at a given value N requires the number of connections per node (i.e. synapses per neuron) to scale proportionally to the Nth root of the number of neurons in the network (Changizi 2001).

In particular, principal neurons, which are sites of great synaptic convergence and divergence, may need to scale up with network size. For example, in larger brains, neocortical pyramidal neuron dendritic arbors increase in size (Bok 1959; Barasa 1960;

Purves 1988; Ramón y Cajal 1995) and in the number of synapses per neuron (O'Kusky and Colonnier 1982; Elston *et al.* 2001; reviewed in DeFelipe *et al.* 2002; Harrison *et al.* 2002). From monkey to human, the increase in number of synapses per neuron has been suggested to support cognitive complexity (Elston *et al.* 2001). However, this increase may well be simply a general scaling consequence of the large absolute size of human brains. If the increase of individual neuronal complexity with respect to total brain size is simply a general scaling relationship that maintains network connectivity, then the relative cognitive complexity of some animals (e.g. chimpanzees, humans, crows, and parrots) may be more appropriately thought of as a function of anomalous total brain size for a given body size (Jerison 1973; Reader and Laland 2002; Burish *et al.* 2004). It will be of interest to ascertain whether the neocortex maintains a constant network diameter across a wide range of mammals.

In nonrecurrent networks such as the cerebellar cortex, which has a multilayered architecture (Marr 1969; Albus 1971), the optimal design of a network may require some of its elements to scale up with overall network size. As described earlier, cerebellar granule cells do not scale with cerebellum size. However, Purkinje cell arbors, which predominantly receive parallel fiber synapses from granule cells, may become larger with brain size (Nieuwenhuys 1967; Eccles 1969; Smolyaninov 1971). Within the mammals in a comparison of rat and cat (Harvey and Napper 1991), the number of spines per Purkinje cell increased from 150 000–175 000 in rat to 300 000–360 000 in cat. This and some structural data from other species (Smolyaninov 1971; Harvey and Napper 1991) indicate that processing in large cerebella maybe made most efficient by scaling up the amount of parallel fiber convergence on each Purkinje cell. What would be optimized by such scaling is not known.

Network degeneracy

Neural computations are performed at the network level. As a result, neurons are adapted to the wider context of the network in which they reside. For example, in the central pattern generator controlling aerial respiration in the slug *Lymnaea stagnalis* (McComb *et al.* 2003), the respiration frequency is higher in adults than in juveniles. However, the neuron initiating rhythmogenesis, RPeD1, scales isometrically over the animal's lifetime, showing a decrease in membrane resistance and an increase in membrane time constant. This modification alone would correspond with decreased excitability in the adult; instead a compensatory increase in synaptic connectivity works to increase rhythmic activity of the pattern generator. More complex tradeoffs can occur as well at a whole-network level. For example, in the lobster stomatogastric system, very different combinations of neuronal parameters can lead to nearly indistinguishable output patterns (Bucher *et al.* 2005). Thus, even in a simple network the large number of degrees of freedom in the system can adapt in many ways to produce a limited range of output patterns.

Brain architecture and species-specific adaptations

The finding that dendritic form scales largely as a function of brain and body size suggests that the differing capabilities of brains in different species would be more likely

to be generated not by varying dendritic and other aspects of neuronal form, but rather by varying the size of a brain or brain region (Kaas 2000). If this is the case, then individual neuronal design may be imposed by a neural architecture's overall layout and absolute size, and added functionality may come about in large part from adding more neurons or modules of neurons. Prominent examples of enhanced function associated with larger region size include the correspondence between cognitive complexity and telencephalic size in mammals (Dunbar 1992; Clark *et al.* 2001) and birds (Lefebvre *et al.* 2002; Burish *et al.* 2004); electrolocation/echolocation and cerebellar volume in mormyrid fishes, bats, and whales (Meek 1992; Clark *et al.* 2001); and song repertoire and volume of song system nuclei in passeriform birds (DeVoogd *et al.* 1993).

In some cases, however, variation in dendritic form may be species-specific. Such specializations might be evident as a departure from the expected scaling relationship. These departures are of particular interest from evolutionary or ethological perspectives. Perhaps as a result, the best evidence for exceptional dendrites has been found in animals with unusual behavioral specializations.

One such type of specialization encompasses acoustic localization, echolocation, and electroreception. In all of these functions, localization of acoustic and electrical stimuli requires calculation of phase differences among signals from multiple sources. Structural adaptations in dendrites may aid in this process biophysically by making the timing of membrane electrical signals particularly precise or fast. In barn owls, which use interaural time and phase differences to locate prey by their sounds, nucleus magnocellularis neurons are more numerous than in other birds (Carr and Boudreau 1993). In addition, magnocellularis and laminaris neurons that are sensitive to higher frequencies have few and short dendrites and thick axons. These differences have been suggested to have the effect of reducing capacitance and increasing the speed of responses. This could be useful in detecting fine differences in the timing of acoustic signals. As another example, mormyrid fish are capable of electroreception. In their exceptionally large 'gigantocerebella', the palisade patterns of Purkinje cell dendrites may be adapted in some way for signal processing via parallel fiber pathways (Meek and Nieuwenhuys 1991). Echolocation, an ability found in cetaceans and insectivorous bats, is accompanied by exceptionally large cerebella (Clark *et al.* 2001); dendrites of cerebellar neurons in these species have not been examined systematically.

Another place in which unusual dendritic specializations may occur is the neocortex of great apes, which show unusual social and cognitive complexity. These animals have several types of giant neocortical neurons, including Betz cells (Sherwood *et al.* 2003), Meynert cells (Sherwood *et al.* 2003), and spindle cells (Nimchinsky *et al.* 1999). These giant cells may have arisen in great apes as extreme adaptations of pyramidal neurons. Among primates, their somata show distinct scaling relationships relative to brain and body size. Like other neocortical pyramidal neurons (Elston *et al.* 2001), they may vary in dendritic extent and synapse number across species as well. At present, however, little is known about their dendrites.

Genetic and developmental constraints influencing dendritic form

Although in animal evolution the unit of natural selection is the individual organism, the primary target upon which selection acts is development. Thus, to better understand the origins of diversity in dendritic structure and to get a feel for what types of changes might occur, we need to consider how changes at the level of DNA can lead to changes in the molecular mechanisms that shape dendrite structure. Here we will emphasize a few points to guide thinking about how morphological changes can arise.

Gene regulatory networks are organized, at least in part, in a hierarchical manner. Genes at the top of such hierarchies may act as 'master control genes' for large-scale developmental programs (Keynes and Krumlauf 1994; Halder *et al.* 1995). For example, the cerebellum and several cerebellar-like structures, including the medial octavolateral nucleus, dorsal octavolateral nucleus, electrosensory lobe, and dorsal cochlear nucleus show striking similarities at both the cellular and network level and originate from one region of the alar plate (Devor 2000; Bell 2002), suggesting that these structures arise from a shared developmental program (Bell 2002). Indeed, small, ectopic, cerebellum-like structures can be induced in the forebrain or midbrain simply by placing beads coated with fibroblast growth factor 8 into developing embryos (Martinez *et al.* 1999). Hierarchical regulation may also regulate modular structures: new neocortical areas have been suggested to arise from the duplication of an existing area by changing a discrete developmental step (Krubitzer 1995; Kaas 2000). Thus, mutations of important developmental genes represent one means of achieving large-scale modifications in brain structure.

Another means of effecting changes in macroscopic and cellular form is mutation that regulates growth rates during development. For example, mutations in *cis*-regulatory DNA elements can have fairly specific effects and have been suggested to be a major source of organ-level morphological evolution (Stern 2000). Application of these concepts at the level of dendritic structure suggests that, depending on the specificity of effect, mutations might be able to affect the scaling of one neuron type or many neuron types at once.

In the case of dendritic form and size, the targets of selection would be mechanisms regulating the growth and maturation of arbors. These mechanisms are studied in several key model systems, including cultured mammalian cells (Craig and Banker 1994; McAllister 2000; Scott and Luo 2001; Whitford *et al.* 2002) and *in vivo* studies of identified neurons from the fruit fly *Drosophila melanogaster* (Gao *et al.* 1999; Gao and Bogert 2003; Grueber and Jan 2004). Thorough reviews of the literature can be found both in this text (see Chapter 3) and elsewhere (Scott and Luo 2001; Cline 2003; Jan and Jan 2003).

Dendrite development can be broken down into four stages: initial dendrite outgrowth, branching, stopping, and pruning and refinement. Here we offer a brief overview of intrinsic and extrinsic mechanisms regulating dendrite shape and size. This overview provides a means for thinking about how developmental mechanisms, shaped by natural selection, might influence dendritic form.

Dendrite outgrowth and branching

The first stage of dendrite growth is the polarization of neurons to generate distinct axonal and dendritic processes. Neurons develop axon-somato-dendritic polarity even in cell culture (for review see Craig and Banker 1994). Even at this early developmental stage, initial process outgrowth can be greatly influenced by extrinsic factors such as growth factors and extracellular matrix proteins (Chamak and Prochiantz 1989; Lein and Higgins 1989; Lein *et al.* 1992; Osterhout *et al.* 1992). As development proceeds, dendrites begin to branch. Diversity of branching structures has been generated by modeling different growth rules (van Pelt *et al.* 1997; Cannon *et al.* 1999), suggesting these rules as a target for selection. Branching patterns can be described in terms of branching probability as a function of distance from the soma, a parameter that can capture differences between complex pyramidal cells and cells of simpler dendritic structure such as various classes of motoneurons and dentate granule cells (van Pelt *et al.* 1997). Two different types of branching events have been observed: splitting of growth cones to generate two new branches, and interstitial branching, the emergence of a new branch from an established dendritic shaft (Bray 1973; Dailey and Smith 1996; Scott and Luo 2001). The first step in interstitial branch formation is the extension of a filopodium from a shaft, which can extend, retract, or become a spine or new branch (Dailey and Smith 1996). In this way a combination of growth and retraction results in an elaborated arbor of branches and spines.

Dendritic growth and branching is affected by both intrinsic and extrinsic factors. Branching is influenced intrinsically by cytoskeletal-associated proteins, small GTPases, transmembrane proteins, and transcription factors (Threadgill *et al.* 1997; Ruchhoeft *et al.* 1999; Lee *et al.* 2000; Li *et al.* 2000; Hakeda-Suzuki *et al.* 2002; Luo 2002; Whitford *et al.* 2002; Gao and Bogert 2003; Emoto *et al.* 2004; Rosso *et al.* 2005) Extrinsic factors include a wide range of neurotrophins, which affect both cell survival and dendritic growth in a neurotrophin and cell type-specific manner (Snider 1988; McAllister *et al.* 1995; 1997). The growth of dendrites proceeds through several stages marked by the appearance of morphological features, and different factors are involved in the regulation of each stage of growth (Scott and Luo 2001).

However, normal branching patterns cannot be entirely replicated in culture. For instance, although Purkinje neurons cocultured with granule cells or densely plated Purkinje cells or neurotrophins (BDNF or NT-4) develop distinctive Purkinje-like arbors (Baptista *et al.* 1994; Morrison and Mason 1998), they do not have the same planar arrangement and appear to branch less frequently. Pyramidal neurons from dissociated hippocampal cultures often fail to form distinct apical and basal dendrites (Dotti *et al.* 1988; Collin *et al.* 1997). This suggests that cultures lack other signaling factors or some other aspect of the normal three-dimensional matrix in which neurons grow.

In addition to branching patterns, another key aspect of a neuron's function is the orientation of its dendrites relative to other neural elements. As in the case of axon guidance, this orientation is established at least in part by chemical cues. One well-studied example is the effect of the diffusible ligand semaphorin 3A. Neocortical pyramidal neurons dendrites grow toward and axons grow away from the cortical plate where

Sem3A is expressed (Giger *et al.* 1996; Polleux *et al.* 1998; Scott and Luo 2001); a similar effect of Sem3A is seen in slice cultures (Polleux *et al.* 1998; 2000). In larger-brained animals, the fact that this gradient should extend over a larger region in space (Gregor *et al.* 2005) may result in larger dendrites.

Stopping

Establishment of a dendritic arbor must include a mechanism for stopping growth. One well-studied example is the effect of contact inhibition on halting the growth of neurons of the same type (homotypic inhibition). A well-known example of tiling is observed in the retina, where the dendrites of some ganglion cell types appear to tile the retina with minimal overlap of neighboring dendritic fields (Wässle *et al.* 1975). Contact inhibition mechanisms are beginning to be investigated in *Drosophila* (Gao *et al.* 2000; Grueber *et al.* 2002; 2003; Emoto *et al.* 2004), *zebrafish* (Sagasti *et al.* 2005) and *C. elegans* (Gallegos and Bargmann 2004). In *Drosophila*, the dendrites of larval medial dorsal (MD) neurons grow until their arbors contact one another around the dorsal midline (Gao *et al.* 2000). Ablation of one MD neuron results in overgrowth of the contralateral surviving neuron. In addition, the dendritic arborization (DA) neurons of the epidermis also exhibit tiling and can be classified into four neuronal subtypes based on their dendritic branching morphologies and tiling rules. Types I and II neurons show homotypic repulsion. Neurons in the third class repel one another only at terminal branches. Neurons of the fourth class show persistent repulsion of all branches (Grueber *et al.* 2002; 2003).

Such stopping mechanisms may provide a means of determining how some dendrites will scale relative to brain size. For example, neuron density has been observed to decrease with increasing brain size (Tower 1954; Lange 1975; reviewed in Harrison *et al.* 2002). Thus, regulation of dendrite growth by intercellular mechanisms would tend to lead to larger dendritic arbors in larger brains. Conversely, because gray matter is composed of closely packed neural elements, stopping mechanisms could affect neuron density itself by regulating the amount of space occupied by dendrites.

Pruning and refinement

Another well-studied type of extrinsic regulation of dendritic form is neural activity (reviewed extensively in Chapter 3). Activity has been shown to influence structural changes including spine addition and retraction (Engert and Bonhoeffer 1999; Trachtenberg *et al.* 2002; Holtmaat *et al.* 2005) as well as larger-scale effects on branch addition and elimination (McAllister *et al.* 1997; Maletic-Savatic *et al.* 1999). In several brain regions it has been observed that synaptic density decreases with age (Purves and Lichtman 1980; Rakic *et al.* 1986; Bourgeois and Rakic 1993; Rakic *et al.* 1994), suggesting that overgrowth occurs during the initial development of dendrites in these brain regions. In many cases, the subsequent pruning of synapses over the course of maturation appears to be activity-dependent (Bock and Braun 1999; Kakizawa *et al.* 2000). The effects of neural activity on structure at the synaptic and on dendritic level seems to be exerted by factors such as neurotrophins and/or other molecules involved in synaptic

plasticity, such as NMDA receptors (Katz and Shatz 1996; McAllister *et al.* 1996; 1997; Bock and Braun 1999).

These developmental mechanisms provide numerous possibilities for the regulation of dendritic form. The dramatic influence of extrinsic factors on dendrite development suggests that these factors may participate in driving the scaling of dendrites with brain and body size. These factors could act independently or in conjunction with neural activity to regulate growth. The role of extrinsic factors also suggests that in larger-brained animals, gradients of diffusible ligands may extend over larger spatial scales; for example, chemoattractive gradients should extend over larger spatial scales in larger brains and perhaps make dendrites grow longer. Intercellular inhibitory mechanisms will also scale if like neurons are spaced farther apart in larger brains. Finally, dendrite development could proceed in a programmed fashion, so that larger dendrites could be generated simply by allowing growth to proceed for a longer period of time.

Epilogue and future directions

In reviewing dendritic variation across species, we have identified three major themes. The first theme is that many neurons and dendrites scale up in size and complexity as a function of overall brain or body size. This scaling is not homogeneous: some cell types show strong scaling and others are nearly constant in form. The second theme is the presence of constraints at the level of cellular and network function that have guided dendritic form. The third theme is the fact that this dendritic diversity has been generated by natural selection acting upon developmental mechanisms. Our review suggests that the study of dendritic optimization and evolution could be advanced by directed work in a number of areas.

Comparative investigations of scaling

The bulk of work on comparative dendritic form has focused on branching patterns. Advances during the last 20 years in the study of synaptic physiology and dendritic function establish a framework within which to examine interspecies variability. Parameters that need to be characterized on a comparative basis are morphological, such as dendrite diameter and spine number; biochemical, such as the abundance and kinetics of signaling molecules; and physiological, such as neuronal firing rates and dendritic integrative properties. These investigations would be directed at the questions of how parameters vary systematically across phylogeny, and what neuronal functional principles are invariant. It would be most advantageous to focus on standard cell types that are already well studied in rodents at all these levels. A prominent candidate would be the pyramidal neuron in either hippocampus or neocortex. Other good choices would include Purkinje neurons and cerebellar granule cells, which are found in nearly all vertebrates and furthermore offer a contrast in scaling properties with one another.

Linkages to animal behavior

A significantly under-investigated area is the linkage of behavioral specializations with variation at a cellular level. In brain regions and cell types with known involvement in

specific behaviors, it should be possible to systematically connect variations in the number of neurons and their anatomical and physiological features with variations in function. One particularly promising target of study is the song system in passeriform birds, in which, at a gross level, the diversity of song repertoire has been demonstrated to be correlated with the size of associated nuclei such as HVc and RA (DeVoogd *et al.* 1993).

Developmental mechanisms

How these variations arose during evolution must ultimately be understood in terms of developmental mechanisms and how they have been selected to generate the diversity of observed forms. The study of dendrite development is an exciting area of research, but at present it is focused on specific model organisms such as *Drosophila* or mouse. Future expansion to consider the variation of developmental mechanisms across species would be greatly illuminating. Of particular interest are the mechanisms that guide the formation of branching patterns such as extension, pruning, and stopping.

Data sharing through online databases

The acquisition of a solid body of data for comparative studies requires measurements of dendritic morphology, protein expression, and physiology across a wide range of species and many different neuronal subtypes. This task is larger than the mission of any one neurobiology laboratory. As more data become available, the need will increase for central repositories for data sharing across laboratories. Not only will this create a larger, more cohesive set of data, but it will also enable subsequent studies by any scientist on parameters not measured in the original work. Several morphology databases currently exist, sponsored by laboratories at Yale (http://senselab.med.yale.edu), the Krasnow Institute for Advanced Study at George Mason University (http://neuromorpho.org), and Duke/Southampton (http://neuron.duke.edu). One database goes beyond morphology to include protein expression: the Cell Centered Database, sponsored by the National Center for Microscopy and Imaging Research at the University of California, San Diego (http://ccdb.ucsd.edu). A notable feature of the Yale database is that it archives the distribution of receptor and channel proteins in the different compartments of the neuron and its dendritic tree for use in a closely linked modelling application, Model DB. Although all the databases are currently dominated by rodent neurons, extension to other animals would be of immense value.

The future availability of comparative information will allow a better understanding of how dendrites have evolved in terms of optimization principles, systems neurobiology, and developmental mechanisms. Ultimately, such an integrated approach may reveal universal functions of dendrites that transcend their functions in any one species.

Acknowledgments

We thank Elizabeth Gould, Josh Morgan, Dale Purves, David Stern, and Charles Stevens for comments and discussion; Geoffrey West and Van Savage for sharing information on

cell size scaling prior to publication; and Lily Johnston and Varun Phadke for providing images of zebra finch, rat, and cat granule cells.

References

Albus JS (1971). A theory of cerebellar function. *Mathematical Biosciences*, **10**, 25–61.

Altman J and Dittmer DS (1961) *Blood and other body fluids*. Federation of American Societies for Experimental Biology, Bethesda, MD.

Alvarez R and Anadon R (1987). The cerebellum of the dogfish, *Scyliorhinus canicula*: a quantitative study. *Journal für Hirnforschung*, **28**, 133–7.

Attwell D and Laughlin SB (2001). An energy budget for signaling in the grey matter of the brain. *Journal of Cerebral Blood Flow and Metabolism*, **21**, 1133–45.

Banavar JR, Maritan A and Rinaldo A (1999). Size and form in efficient transportation networks. *Nature*, **399**, 130–2.

Baptista CA, Hatten ME, Blazeski R and Mason CA (1994). Cell–cell interactions influence survival and differentiation of purified Purkinje cells in vitro. *Neuron*, **12**, 243–60.

Barasa A (1960). [Form, size and density of the neurons in the cerebral cortex of mammals of different body sizes.]. *Zeitschrift für Zellforschung und mikroskopische Anatomie*, **53**, 69–89.

Barrett JN and Crill WE (1974a). Influence of dendritic location and membrane properties on the effectiveness of synapses on cat motoneurons. *Journal of Physiology*, **239**, 325–45.

Barrett JN and Crill WE (1974b). Specific membrane properties of cat motoneurons. *Journal of Physiology*, **239**, 301–24.

Bekkers JM and Stevens CF (1990). Two different ways evolution makes neurons larger. *Progress in Brain Research*, **83**, 37–45.

Bell CC (2002). Evolution of cerebellum-like structures. *Brain, Behavior and Evolution*, **59**, 312–26.

Bloedel JR and Bracha V (1998). Current concepts of climbing fiber function. *Anatomical Record,* **253**, 118–26.

Bock J and Braun K (1999). Blockade of N-methyl-D-aspartate receptor activation suppresses learning-induced synaptic elimination. *Proceedings of the National Academy of Sciences of the United States of America*, **96**, 2485–90.

Bok ST (1959). *Histonomy of the cerebral cortex*. Elsevier, Amsterdam.

Bourgeois JP and Rakic P (1993). Changes of synaptic density in the primary visual cortex of the macaque monkey from fetal to adult stage. *Journal of Neuroscience*, **13**, 2801–20.

Braekevelt CR (1998). Fine structure of the retinal photoreceptors of the emu (*Dromaius novaehollandiae*). *Tissue and Cell*, **30**, 137–48.

Bray D (1973). Branching patterns of individual sympathetic neurons in culture. *Journal of Cell Biology*, **56**, 702–12.

Brown TH, Chapman PF, Kairiss EW and Keenan CL (1988). Long-term synaptic potentiation. *Science*, **242**, 724–8.

Bucher D, Prinz AA and Marder E (2005). Animal-to-animal variability in motor pattern production in adults and during growth. *Journal of Neuroscience*, **25**, 1611–19.

Buckmaster PS and Amaral DG (2001). Intracellular recording and labeling of mossy cells and proximal CA3 pyramidal cells in macaque monkeys. J Comp Neurol **430**, 264–81.

Buckmaster PS, Alonso A, Canfield DR and Amaral DG (2004). Dendritic morphology, local circuitry, and intrinsic electrophysiology of principal neurons in the entorhinal cortex of macaque monkeys. *Journal of Comparative Neurology*, **470**, 317–29.

Burish MJ, Kueh HY and Wang SS (2004). Brain architecture and social complexity in modern and ancient birds. *Brain, Behavior and Evolution*, **63**, 107–24.

Cai X, Liang CW, Muralidharan S, Kao JP, Tang CM and Thompson SM (2004). Unique roles of SK and Kv4.2 potassium channels in dendritic integration. *Neuron*, **44**, 351–64.

Cannon RC, Wheal HV and Turner DA (1999). Dendrites of classes of hippocampal neurons differ in structural complexity and branching patterns. *Journal of Comparative Neurology*, **413**, 619–33.

Carr CE and Boudreau RE (1993). Organization of the nucleus magnocellularis and the nucleus laminaris in the barn owl: encoding and measuring interaural time differences. *Journal of Comparative Neurology*, **334**, 337–55.

Chamak B and Prochiantz A (1989). Influence of extracellular matrix proteins on the expression of neuronal polarity. *Development*, **106**, 483–91.

Changizi MA (2001). Principles underlying mammalian neocortical scaling. *Biological Cybernetics*, **84**, 207–15.

Cherniak C (1994). Component placement optimization in the brain. *Journal of Neuroscience*, **14**, 2418–27.

Chklovskii DB (2000). Optimal sizes of dendritic and axonal arbors in a topographic projection. *Journal of Neurophysiology*, **83**, 2113–19.

Chklovskii DB (2004). Synaptic connectivity and neuronal morphology: two sides of the same coin. *Neuron*, **43**, 609–17.

Chklovskii DB and Stevens CF (2000). Wiring optimization in the brain. *Advances in Neural Information Processing Systems*, **12**, 103–07.

Clark DA, Mitra PP and Wang SS-H (2001). Scalable architecture in mammalian brains. *Nature*, **411**, 189–93.

Cline H (2003) Sperry and Hebb: oil and vinegar? *Trends in Neurosciences*, **26**, 655–61.

Collin C, Miyaguchi K and Segal M (1997). Dendritic spine density and LTP induction in cultured hippocampal slices. *Journal of Neurophysiology*, **77**, 1614–23.

Craig AM and Banker G (1994). Neuronal polarity. *Annual Review of Neuroscience*, **17**, 267–310.

Dailey ME and Smith SJ (1996). The dynamics of dendritic structure in developing hippocampal slices. *Journal of Neuroscience*, **16**, 2983–94.

DeFelipe J, Alonso-Nanclares L and Arellano JI (2002). Microstructure of the neocortex: comparative aspects. *Journal of Neurocytology*, **31**, 299–316.

DeVoogd TJ, Krebs JR, Healy SD and Purvis A (1993). Relations between song repertoire size and the volume of brain nuclei related to song: comparative evolutionary analyses amongst oscine birds. *Proceedings of the Royal Society of London. Series B*, **254**, 75–82.

Devor A (2000). Is the cerebellum like cerebellar-like structures? *Brain Research. Brain Research Reviews*, **34**, 149–56.

Dityatev A, Birinyi A, Puskar Z, Antal M and Clamann HP (2001). A correlative physiological and morphological analysis of monosynaptically connected propriospinal axon-motoneuron pairs in the lumbar spinal cord of frogs. *Neuroscience*, **106**, 405–17.

Dotti CG, Sullivan CA and Banker GA (1988). The establishment of polarity by hippocampal neurons in culture. *Journal of Neuroscience*, **8**, 1454–68.

Dryer L and Graziadei PP (1994). Mitral cell dendrites: a comparative approach. *Anatomy and Embryology*, **189**, 91–106.

Dunbar RIM (1992). Neocortex size as a constraint on group size in primates. *Journal of Human Evolution*, **20**, 469–93.

Ebbesson SOE (1968a). Quantitative studies of superior cervical sympathetic ganglia in a variety of primates including man. II. Neuronal packing density. *Journal of Morphology*, **124**, 181–6.

Ebbesson SOE (1968b). Quantitative studies of superior cervical sympathetic ganglia in a variety of primates including man. I. The ratio of preganglionic fibers to ganglionic neurons. *Journal of Morphology*, **124**, 117–32.

Eccles JC (1969). The development of the cerebellum of vertebrates in relation to the control of movement. *Naturwissenschaften*, **56**, 525–34.

Edwards DH, Yeh SR, Barnett LD and Nagappan PR (1994). Changes in synaptic integration during the growth of the lateral giant neuron of crayfish. *Journal of Neurophysiology*, **72**, 899–908.

Elston GN, Benavides-Piccione R and DeFelipe J (2001). The pyramidal cell in cognition: a comparative study in human and monkey. *Journal of Neuroscience*, **21**, RC163.

Emoto K, He Y, Ye B *et al.* (2004). Control of dendritic branching and tiling by the Tricornered-kinase/Furry signaling pathway in *Drosophila* sensory neurons. *Cell*, **119**, 245–56.

Engert F and Bonhoeffer T (1999). Dendritic spine changes associated with hippocampal long-term synaptic plasticity. *Nature*, **399**, 66–70.

Forehand CJ (1985). Density of somatic innervation on mammalian autonomic ganglion cells is inversely related to dendritic complexity and preganglionic convergence. *Journal of Neuroscience*, **5**, 3403–8.

Gallegos ME and Bargmann CI (2004). Mechanosensory neurite termination and tiling depend on SAX-2 and the SAX-1 kinase. *Neuron*, **44**, 239–49.

Gao FB and Bogert BA (2003). Genetic control of dendritic morphogenesis in *Drosophila*. *Trends in Neurosciences*, **26**, 262–8.

Gao FB, Brenman JE, Jan LY and Jan YN (1999). Genes regulating dendritic outgrowth, branching, and routing in *Drosophila*. *Genes and Development*, **13**, 2549–61.

Gao FB, Kohwi M, Brenman JE, Jan LY and Jan YN (2000). Control of dendritic field formation in *Drosophila*: the roles of flamingo and competition between homologous neurons. *Neuron*, **28**, 91–101.

Giger RJ, Wolfer DP, De Wit GM and Verhaagen J (1996). Anatomy of rat semaphorin III/collapsin-1 mRNA expression and relationship to developing nerve tracts during neuroembryogenesis. *Journal of Comparative Neurology*, **375**, 378–92.

Gilly WF, Gillette R and McFarlane M (1997). Fast and slow activation kinetics of voltage-gated sodium channels in molluscan neurons. *Journal of Neurophysiology*, **77**, 2373–84.

Golding NL, Staff NP and Spruston N (2002). Dendritic spikes as a mechanism for cooperative long-term potentiation. *Nature*, **418**, 326–31.

Gregor T, Bialek W, de Ruyter van Steveninck RR, Tank DW and Wieschaus EF (2005). Diffusion and scaling during early embryonic pattern formation. Proceedings of the National Academy of Sciences of the United States of America, **102**, 18403–7.

Grueber WB and Jan YN (2004). Dendritic development: lessons from *Drosophila* and related branches. *Current Opinion in Neurobiology*, **14**, 74–82.

Grueber WB, Jan LY and Jan YN (2002). Tiling of the *Drosophila* epidermis by multidendritic sensory neurons. *Development*, **129**, 2867–78.

Grueber WB, Ye B, Moore AW, Jan LY and Jan YN (2003). Dendrites of distinct classes of *Drosophila* sensory neurons show different capacities for homotypic repulsion. Current Biology, **13**, 618–26.

Hakeda-Suzuki S, Ng J, Tzu J *et al.* (2002). Rac function and regulation during *Drosophila* development. *Nature*, **416**, 438–42.

Halder G, Callaerts P and Gehring WJ (1995). Induction of ectopic eyes by targeted expression of the eyeless gene in Drosophila. *Science*, **267**, 1788–92.

Harrison KH, Hof PR and Wang SS-H (2002). Scaling laws in the mammalian neocortex: does form provide clues to function? *Journal of Neurocytology*, **31**, 289–98.

Harvey RJ and Napper RMA (1991). Quantitative studies on the mammalian cerebellum. *Progress in Neurobiology*, **36**, 437–63.

Häusser M, Major G and Stuart GJ (2001). Differential shunting of EPSPs by action potentials. *Science*, **291**, 138–41.

Hebb DO (1949). Organization of behavior: a neuropsychological theory. Wiley, New York.

Hill AAV, Edwards DH and Murphey RK (1994). The effect of neuronal growth on synaptic integration. *Journal of Computational Neuroscience*, **1**, 239–54.

Hillman DE (1979). Neuronal shape parameters and substructures as a basis of neuronal form. In G Adelman and BH Smith, eds. *Neurosciences: fourth study program*, pp. 477–98. MIT Press, Cambridge, MA.

Holtmaat AJ, Trachtenberg JT, Wilbrecht L *et al.* (2005). Transient and persistent dendritic spines in the neocortex in vivo. *Neuron*, **45**, 279–91.

Hume RI and Purves D (1983). Apportionment of the terminals from single preganglionic axons to target neurones in the rabbit ciliary ganglion. *Journal of Physiology*, **338**, 259–75.

Huxley J (1932). *Problems of relative growth*. Methuen, London.

Ivanov A and Purves D (1989). Ongoing electrical activity of superior cervical ganglion cells in mammals of different size. *Journal of Comparative Neurology*, **284**, 398–404.

Jan Y-N and Jan LY (2003). The control of dendrite development. *Neuron*, **40**, 229–42.

Jerison HJ (1973). *Evolution of the brain and intelligence*. Academic Press, New York.

Kaas JH (2000). Why is brain size so important: design problems and solutions as neocortex gets bigger or smaller. *Brain and Mind*, **1**, 7–23.

Kakizawa S, Yamasaki M, Watanabe M and Kano M (2000). Critical period for activity-dependent synapse elimination in developing cerebellum. *Journal of Neuroscience*, **20**, 4954–61.

Katz LC and Shatz CJ (1996). Synaptic activity and the construction of cortical circuits. *Science*, **274**, 1133–8.

Keynes R and Krumlauf R (1994). Hox genes and regionalization of the nervous system. *Annual Review of Neuroscience*, **17**, 109–32.

Kötter R and Feizelmeier M (1998). Species-dependence and relationship of morphological and electrophysiological properties in nigral compacta neurons. *Progress in Neurobiology*, **54**, 619–32.

Krubitzer L (1995). The organization of neocortex in mammals: are species differences really so different? *Trends in Neurosciences*, **18**, 408–17.

Lange W (1975). Cell number and cell density in the cerebellar cortex of man and some other mammals. *Cell and Tissue Research*, **157**, 115–24.

Lee T, Winter C, Marticke SS, Lee A and Luo L (2000). Essential roles of *Drosophila* RhoA in the regulation of neuroblast proliferation and dendritic but not axonal morphogenesis. *Neuron*, **25**, 307–16.

Lefebvre L, Nicolakakis N and Boire D (2002). Tools and brains in birds. *Behaviour*, **135**, 1077–97.

Lein PJ and Higgins D (1989). Laminin and a basement membrane extract have different effects on axonal and dendritic outgrowth from embryonic rat sympathetic neurons in vitro. *Developmental Biology*, **136**, 330–45.

Lein PJ, Banker GA and Higgins D (1992). Laminin selectively enhances axonal growth and accelerates the development of polarity by hippocampal neurons in culture. *Brain Research. Developmental Brain Research*, **69**, 191–7.

Levi G (1905). Studi sulla grandezza delle cellule. *Archivio italiano di anatomia e di embriologia*, **5**, 291–358.

Li Z, Van Aelst L and Cline HT (2000). Rho GTPases regulate distinct aspects of dendritic arbor growth in *Xenopus* central neurons in vivo. *Nature Neuroscience*, **3**, 217–25.

Lichtman JW and Purves D (1980). The elimination of redundant preganglionic innervation to hamster sympathetic ganglion cells in early post-natal life. *Journal of Physiology*, **301**, 213–28.

Lichtman JW, Purves D and Yip JW (1980). Innervation of sympathetic neurones in the guinea-pig thoracic chain. *Journal of Physiology*, **298**, 285–99.

Lledo PM, Zhang X, Sudhof TC, Malenka RC and Nicoll RA (1998). Postsynaptic membrane fusion and long-term potentiation. *Science*, **279**, 399–403.

Llinás R, ed (1969). *Neurobiology of cerebellar evolution and development*. American Medical Association, Chicago.

Llinás R and Sugimori M (1980). Electrophysiological properties of in vitro Purkinje cell dendrites in mammalian cerebellar slices. *Journal of Physiology*, **305**, 197–213.

Luo L (2002). Actin cytoskeleton regulation in neuronal morphogenesis and structural plasticity. *Annual Review of Cell and Developmental Biology*, **18**, 601–35.

Lux HD, Schubert P and Kreutzberg GW (1970). Direct matching of morphological and electrophysiological data in cat spinal motoneurons. In P Anderson and JKI Kansen, eds. *Excitatory synaptic mechanisms*. Universitetsforlaget, Oslo.

Magee JC and Johnston D (1997). A synaptically controlled, associative signal for Hebbian plasticity in hippocampal neurons. *Science*, **275**, 209–13.

Malenka RC and Nicoll RA (1999). Long-term potentiation — a decade of progress? *Science*, **285**, 1870–4.

Maletic-Savatic M, Malinow R and Svoboda K (1999). Rapid dendritic morphogenesis in CA1 hippocampal dendrites induced by synaptic activity. *Science*, **283**, 1923–7.

Markram H, Lübke J, Frotscher M and Sakmann B (1997). Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science*, **275**, 213–15.

Marr D (1969). A theory of cerebellar cortex. *Journal of Physiology*, **202**, 437–70.

Martinez S, Crossley PH, Cobos I, Rubenstein JL and Martin GR (1999). FGF8 induces formation of an ectopic isthmic organizer and isthmocerebellar development via a repressive effect on Otx2 expression. *Development*, **126**, 1189–1200.

McAllister AK (2000). Cellular and molecular mechanisms of dendrite growth. *Cerebral Cortex*, **10**, 963–73.

McAllister AK, Lo DC and Katz LC (1995). Neurotrophins regulate dendritic growth in developing visual cortex. *Neuron*, **15**, 791–803.

McAllister AK, Katz LC and Lo DC (1996). Neurotrophin regulation of cortical dendritic growth requires activity. *Neuron*, **17**, 1057–64.

McAllister AK, Katz LC and Lo DC (1997). Opposing roles for endogenous BDNF and NT-3 in regulating cortical dendritic growth. *Neuron*, **18**, 767–78.

McComb C, Meems R, Syed N and Lukowiak K (2003). Electrophysiological differences in the CpG aerial respiratory behavior between juvenile and adult *Lymnaea*. *Journal of Neurophysiology*, **90**, 983–92.

Meek J (1992). Comparative aspects of cerebellar organization: from mormyrids to mammals. *European Journal of Morphology*, **30**, 37–51.

Meek J and Nieuwenhuys R (1991). Palisade pattern of mormyrid Purkinje cells: a correlated light and electron microscopic study. *Journal of Comparative Neurology*, **306**, 156–92.

Morrison ME and Mason CA (1998). Granule neuron regulation of Purkinje cell development: striking a balance between neurotrophin and glutamate signaling. *Journal of Neuroscience*, **18**, 3563–73.

Nicholson C, Llinas R and Precht W (1969). Neural elements of the cerebellum in elasmobranch fishes: Structural and functional characteristics. In R Llinas, ed. *Neurobiology of cerebellar evolution and development*, pp. 215–43. American Medical Association, Chicago.

Nieuwenhuys R (1967). Comparative anatomy of the cerebellum. In CA Fox and RS Snider, eds. *Progress in brain research*, vol. 25, pp. 1–93. Elsevier, Amsterdam.

Nieuwenhuys R, ten Donkelaar H and Nicholson C (1998). *The central nervous system of vertebrates*. Springer, Berlin.

Nimchinsky EA, Gilissen E, Allman JM, Perl DP, Erwin JM and Hof PR (1999). A neuronal morphologic type unique to humans and great apes. *Proceedings of the National Academy of Sciences of the United States of America*, **96**, 5268–73.

O'Kusky J and Colonnier M (1982). A laminar analysis of the number of neurons, glia, and synapses in the visual cortex (area 17) of adult macaque monkeys. *Journal of Comparative Neurology*, **210**, 278–90.

Ohara PT and Havton LA (1994). Preserved features of thalamocortical projection neuron dendritic architecture in the somatosensory thalamus of the rat, cat and macaque. *Brain Research*, **648**, 59–264.

Olsen O, Nadim F, Hill AA and Edwards DH (1996). Uniform growth and neuronal integration. *Journal of Neurophysiology*, **76**, 1850–7.

Osterhout DJ, Frazier WA and Higgins D (1992). Thrombospondin promotes process outgrowth in neurons from the peripheral and central nervous systems. *Developmental Biology*, **150**, 256–65.

Palay SL and Chan-Palay V (1974). *Cerebellar cortex: cytology and organization*. Springer, Berlin.

Picones A, Chung SC and Korenbrot JI (2003). Developmental maturation of passive electrical properties in retinal ganglion cells of rainbow trout. *Journal of Physiology*, **548**, 71–83.

Polleux F, Morrow T and Ghosh A (2000). Semaphorin 3A is a chemoattractant for cortical apical dendrites. *Nature*, **404**, 567–73.

Polleux F, Giger RJ, Ginty DD, Kolodkin AL and Ghosh A (1998). Patterning of cortical efferent projections by semaphorin-neuropilin interactions. *Science*, **282**, 1904–6.

Polsky A, Mel BW and Schiller J (2004). Computational subunits in thin dendrites of pyramidal cells. *Nature Neuroscience*, **7**, 621–7.

Purves D (1988). *Body and brain: a trophic theory of neural connections*. Harvard University Press, Cambridge, MA.

Purves D and Lichtman JW (1980). Elimination of synapses in the developing nervous system. *Science*, **210**, 153–7.

Purves D and Hume RI (1981). The relation of postsynaptic geometry to the number of presynaptic axons that innervate autonomic ganglion cells. *Journal of Neuroscience*, **1**, 441–52.

Purves D and Lichtman JW (1985). Geometrical differences among homologous neurons in mammals. *Science*, **228**, 298–302.

Purves D, Rubin E, Snider WD and Lichtman JW (1986). Relation of animal size to convergence, divergence and neuronal number in peripheral sympathetic pathways. *Journal of Neuroscience*, **6**, 158–63.

Rakic P, Bourgeois JP and Goldman-Rakic PS (1994). Synaptic development of the cerebral cortex: implications for learning, memory, and mental illness. *Progress in Brain Research*, **102**, 227–43.

Rakic P, Bourgeois J-P, Eckenhoff MF, Zecevic N and Goldman-Rakic P (1986). Concurrent overproduction of synapses in diverse regions of the primate cerebral cortex. *Science*, **232**, 232–5.

Rall W (1977). Core conductor theory and cable properties of neurons. In ER Kandel, ed. *Handbook of physiology*, The nervous system, cellular biology of neurons. Sect. 1, pp. 39–98. American Physiological Society, Bethesda, MD.

Ramón y Cajal S (1995). *Histology of the nervous system of man and vertebrates*. Oxford University Press, Oxford.

Raymond JL, Lisberger SG and Mauk MD (1996). The cerebellum: a neuronal learning machine? Science **272**, 1126–31.

Reader SM and Laland KN (2002). Social intelligence, innovation, and enhanced brain size in primates. *Proceedings of the National Academy of Sciences of the United States of America*, **99**, 4436–41.

Ringo JL (1991). Neuronal interconnection as a function of brain size. *Brain, Behavior and Evolution*, **38**, 1–6.

Rojas LM, Ramirez Y, McNeil R, Mitchell M and Marin G (2004). Retinal morphology and electrophysiology of two caprimulgiformes birds: the cave-living and nocturnal oilbird (*Steatornis caripensis*), and the crepuscularly and nocturnally foraging common pauraque (*Nyctidromus albicollis*). *Brain, Behavior and Evolution*, **64**, 19–33.

Rosso SB, Sussman D, Wynshaw-Boris A and Salinas PC (2005). Wnt signaling through Dishevelled, Rac and JNK regulates dendritic development. *Nature Neuroscience*, **8**, 34–42.

Ruchhoeft ML, Ohnuma S, McNeill L, Holt CE and Harris WA (1999). The neuronal architecture of *Xenopus* retinal ganglion cells is sculpted by rho-family GTPases in vivo. *Journal of Neuroscience*, **19**, 8454–63.

Sagasti A, Guido GR, Raible DW and Schier AF (2005). Repulsive interactions shape the morphologies and functional arrangement of zebrafish peripheral sensory arbors. *Current Biology*, **15**, 804–14.

Savage VM, Allen AP, Brown JH, Gillooly JF, German AB, Woodruff WH and West GB (2007). Scaling of number, size, and metabolic rate of cells with body size in mammals. Proceedings of the National Academy of Sciences of the United States of America, **104**, 4718–23.

Schaper A (1898). The finer structure of the selachian cerebellum (*Mustelus vulgaris*) as shown by chrome-silver preparations. *Journal of Comparative Neurology*, **8**, 1–20.

Schüz A and Demianenko GP (1995). Constancy and variability in cortical structure. A study on synapses and dendritic spines in hedgehog and monkey. *Journal für Hirnforschung*, **36**, 113–22.

Scott EK and Luo L (2001). How do dendrites take their shape? *Nature Neuroscience*, **4**, 359–65.

Sherwood CC, Lee PW, Rivara CB *et al.* (2003). Evolution of specialized pyramidal neurons in primate visual and motor cortex. *Brain, Behavior and Evolution*, **61**, 28–44.

Smolyaninov VV (1971). Some special features of organization of the cerebellar cortex. In IM Gelfand, VS Gurfinkel, SV Fomin and ML Tsetlin, eds. *Models of the structural-functional organization of certain biological systems*, pp. 251–325. MIT Press, Cambridge, MA.

Snider WD (1987). The dendritic complexity and innervation of submandibular neurons in five species of mammals. *Journal of Neuroscience*, **7**, 1760–8.

Snider WD (1988). Nerve growth factor enhances dendritic arborization of sympathetic ganglion cells in developing mammals. *Journal of Neuroscience*, **8**, 2628–34.

St. John JL, Rosene DL and Luebke JI (1997). Morphology and electrophysiology of dentate granule cells in the rhesus monkey: comparison with the rat. *Journal of Comparative Neurology*, **387**, 136–47.

Sterling P (1997). Retina. In GM Shepherd, ed. *The synaptic organization of the brain*, 4th edn, p. 656. Oxford University Press, New York.

Sterling P (2003). How retinal circuits optimize the transfer of visual information. In LM Chalupa and JS Werner, eds. *The visual neurosciences*, pp. 234–59. MIT Press, Cambridge, MA.

Stern DL (2000). Evolutionary developmental biology and the problem of variation. *Evolution; International Journal of Organic Evolution*, **54**, 1079–91.

Teissier G (1939). Biometrie de la cellule. *Tabulae*, **19**, 1–64.

Tepper JM, Damlama M and Trent F (1994). Postnatal changes in the distribution and morphology of rat substantia nigra dopaminergic neurons. *Neuroscience*, **60**, 469–77.

Thompson DW (1942). *On growth and form*. Cambridge University Press, Cambridge.

Threadgill R, Bobb K and Ghosh A (1997). Regulation of dendritic growth and remodeling by Rho, Rac, and Cdc42. *Neuron*, **19**, 625–34.

Tower DB (1954). Structural and functional organization of mammalian cerebral cortex: the correlation of neurone density with brain size. *Journal of Comparative Neurology*, **101**, 9–52.

Trachtenberg JT, Chen BE, Knott GW *et al.* (2002). Long-term in vivo imaging of experience-dependent synaptic plasticity in adult cortex. *Nature*, **420**, 788–94.

Van Essen DC (1997). A tension-based theory of morphogenesis and compact wiring in the central nervous system. *Nature*, **385**, 313–18.

van Pelt J, Dityatev AE and Uylings HB (1997). Natural variability in the number of dendritic segments: model-based inferences about branching during neurite outgrowth. *Journal of Comparative Neurology*, **387**, 325–40.

Wässle H, Levick WR, Kirk DL and Cleland BG (1975). Axonal conduction velocity and perikaryal size. *Experimental Neurology*, **49**, 246–51.

West GB, Brown JH and Enquist BJ (1997). A general model for the origin of allometric scaling laws in biology. *Science*, **276**, 122–6.

Whitford KL, Dijkhuizen P, Polleux F and Ghosh A (2002). Molecular control of cortical dendrite development. *Annual Review of Neuroscience*, **25**, 127–49.

Yelnik JF, Francois C, Percheron G and Heyner S (1987). Golgi study of the primate substantia nigra. I. Quantitative morphology and typology of nigral neurons. *Journal of Comparative Neurology*, **265**, 455–72.

Zhang K and Sejnowski TJ (2000). A universal scaling law between gray matter and white matter of cerebral cortex. *Proceedings of the National Academy of Sciences of the United States of America*, **97**, 5621–6.