Cortical Areas: Unity and Diversity

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6 Regional Dendritic Variation in Primate Cortical Pyramidal Cells

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This chapter reviews quantitative neuromorphological investigations of primate neocortex. In particular, we explore regional variation in the basal dendritic and spine systems of pyramidal neurones. This synthesis indicates a relatively consistent, stepwise increase in dendritic extent and spine number in a caudal-rostral direction. Cortical regions involved in the early stages (e.g. primary sensory areas) of processing generally exhibit less complex dendritic/spine systems than those regions involved in the latter stages of information processing (e.g. prefrontal cortex). This dendritic progression appears to reflect significant differences in the nature of cortical processing, with spine-dense neurones at hierarchically higher association levels integrating a broader range of synaptic input than those at lower cortical levels. In concluding the chapter, we consider the characteristics of the receptive dendritic membrane of individual neuronal elements (e.g. voltage-gated channels, input resistance, voltage attenuation) and how such factors may relate to cortical computation.

KEYWORDS: cerebral cortex, dendrite, quantitative, regional variation, spine

1. INTRODUCTION

This chapter considers the degree to which neurones in different areas of the primate cerebral cortex vary with regard to the extent and complexity of their dendritic ensembles. We focus here on pyramidal neurones because they are the principal component of neocortical circuitry. Moreover, we limit our discussion to the basal dendrite ensembles of pyramidal cells, and thus follow the precedent set in most quantitative studies of cortical neurones (Schlaug *et al.*, 1993). Since the horizontal components of the pyramidal cell ensemble, and notably the basal dendrites, provide the main receptive surface for axons of intracortical origin (Globus and Scheibel, 1967a,b,c), there is a robust anatomical basis for this choice. In addition, the enormous morphological variation of the stellate and non-pyramidal cell contingents has always made these fascinating elements more problematic for quantitative evaluation (see Prinz *et al.*, 1997; Seldon, 1982).

In the last century, the classic qualitative studies of Golgi (1886), Cajal (1909), and Lorente de Nó (1922), among others, provided the structural framework for a brilliant

period of descriptive structuro-functional studies of the cerebral hemispheres. But as we leave the decade of the brain and enter the 21st century, a more discriminating and computationally knowledgeable group of investigators poses questions that demand information with higher levels of resolution. The intimate organization of dendrite membrane patches, the structure, placement, and dimensions of individual dendrite spines, the length and orientation of dendrite tips, and so on, become data necessary for a more profound understanding of the structuro-functional basis of neural computation.

In what follows, we attempt an overview of several quantitative approaches to analysis of cortical dendrites as seen from an end-of-the-century point of view. We lean heavily upon our own Golgi-based studies of human cortices with the following justifications: (1) We are probably more aware of the shortcomings of our own work than of others'; and (2) the field of quantitative human neural morphology is still very young with relatively few published investigations. The major thrust of this overview is to provide evidence relating dendritic length and spine number to cortical area; in general, the more complex the computational functions of the area, the longer the dendrites and the more numerous the spines. This relationship may be meaningful in terms of what is known about the underlying physiology of dendrites and their spines, and may reflect significant regional differences in the nature of cortical processing.

2. QUANTITATIVE TECHNIQUES AND METHODOLOGICAL CONSIDERATIONS

Comparisons across neuromorphological studies are somewhat problematic because each quantitative technique exhibits its own strengths and weaknesses (for review, see Uylings *et al.*, 1975, 1986). Moreover, all quantitative neuromorphological investigations face formidable methodological constraints.

2.1. Quantitative Techniques

With considerable histological and technological advances over the last few decades, several quantitative methodologies have emerged. At present, three morphological techniques are commonly employed for dendritic quantification. The oldest and most widely used is the *semi-quantitative analysis of Sholl* (1953, 1956), whereby a series of equidistant, concentric rings are superimposed over a (typically traced) neurone, allowing the number of dendritic intersections per ring to be counted (see Figure 6.1A, 6.1B). In the Eayrs' (1955) concentric circle variation of this technique, the researcher also quantifies the number of bifurcations and terminal endings within each ring. As such, these techniques do not quantify dendritic segments in great detail, but do provide a first order approximation of the overall dendritic profile.

The second technique, *a metric reconstruction*, involves tracing the dendritic tree, branch by branch, and measuring the length (and possibly diameter) of each segment (see Figure 6.1C, 6.1D). This can be accomplished either indirectly by tracing cells with a camera lucida and entering the coordinates on a digitizing tablet, or directly by quantifying neurones through a microscope interfaced with a computer system (e.g. the Neurolucida system, MicroBrightfield, Inc.). Although older versions of this technique were somewhat limited, most recent versions can reconstruct accurately the entire dendritic ensemble in 3-dimensional space, and can also provide estimates of spine number/density.

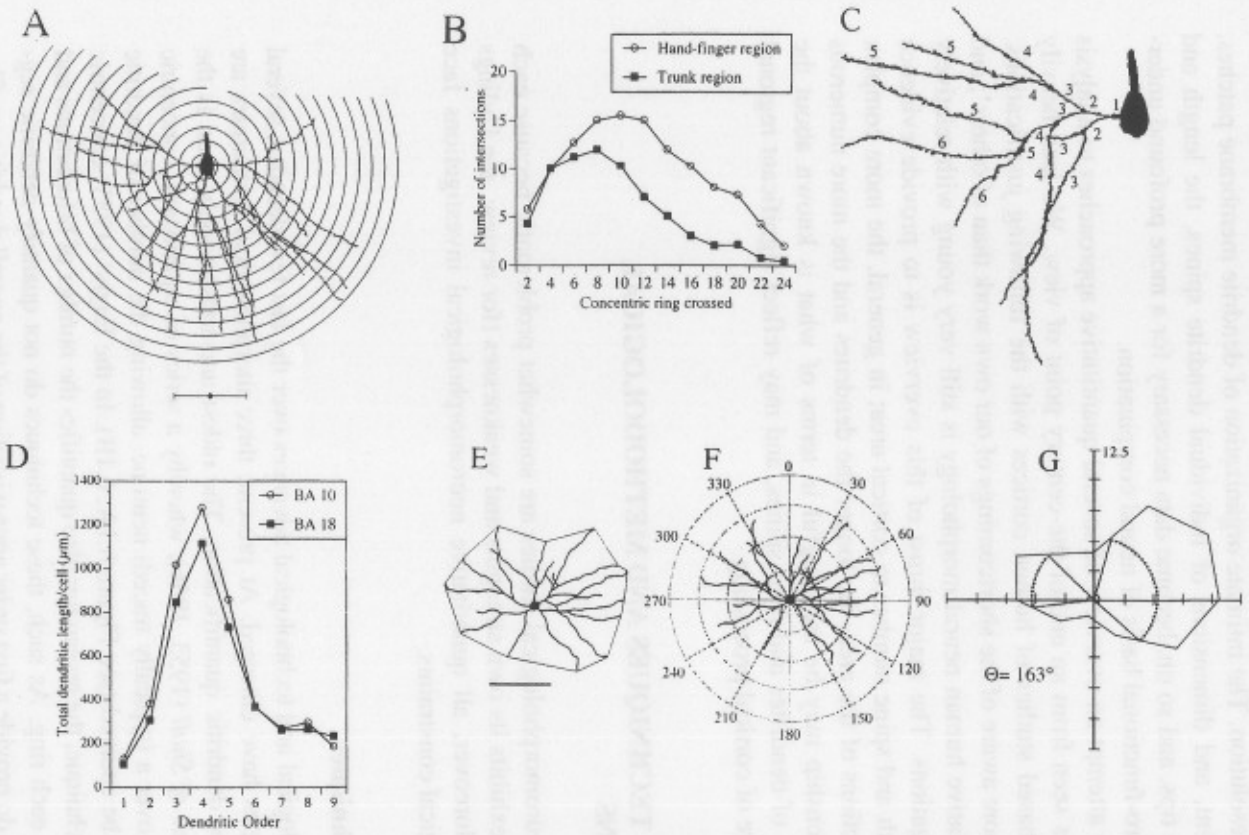

Figure 6.1. Illustrative depictions of common neuromorphological quantitative techniques. **(A)** Sample supragranular pyramidal cell (scale bar = 100 μm) with Sholl concentric rings superimposed. **(B)** Results of a Sholl analysis within one individual comparing the basal dendritic systems in the trunk and hand-finger region of the somatosensory cortex. Note the relatively more complex dendrites in the hand-finger region compared with the trunk region, as determined by the higher number of concentric ring crossings (adapted from Scheibel *et al.*, 1990). **(C)** A metric reconstruction of individual basal dendritic segments, which are traced here in a somatofugal pattern. **(D)** Results of such a metric reconstruction illustrating a greater total dendritic length in prefrontal (BA10) compared with occipital (BA18) pyramidal neurones (adapted from Jacobs *et al.*, 1997). **(E)** Sample basal dendritic system (tangential view from the pial surface) with a polygon (hull) around dendritic tips (scale bar = 100 μm). This analysis provides a rough estimate of dendritic field size. **(F)** A modified Sholl analysis is performed by superimposing concentric rings with 30° polar angle intervals, resulting in a polar plot **(G)** of dendritic tree intersections as a function of direction from the soma. This polar plot provides a measure of dendritic tree orientation. In order to quantify the degree of dendritic bias, the researchers calculate the sum of the angles (q) subtended between a circle (radius equal to the half-maximal value of the polar plot) and the polar plot. Cells with tightly clustered dendritic trees have low q values: those with no bias have q value near 360° (**E**, **F** and **G**: adapted from Elston *et al.*, 1998b).

Such analyses permit a fine-level, topographical depiction (e.g. length, number, and volume) of individual dendritic segments, and allow these segments to be integrated somatofugally (Van der Loos, 1959) within the 3-dimensional geometry of the dendritic array.

The third technique examines the *dendritic field* of the neurone (see Figure 6.1E), an idea first investigated in a quantitative manner by Colonnier (1964). To examine the overall area of the dendritic field, researchers draw a polygon (hull) that joins the distal tips of the outermost dendrites, and calculate the enclosed area. This technique provides a relatively simple estimate of dendritic spread, but does not address overall complexity of branching. To estimate such complexity, along with the clustering and orientation of the dendritic tree, researchers can employ a modified Sholl analysis, which involves (1) comparing the overall number of intersections per concentric ring, and (2) examining the distribution of intersections as a function of the radial position of the dendrite relative to the soma, and depicting these in polar plots (see Figure 6.1F, 6.1G). This has been a particularly useful technique for investigating the geometry of the domains of dendritic trees in different cortical regions.

2.2. Methodological Considerations

Extensive quantitative neuromorphological research has been conducted on non-human organisms (e.g. Valverde, 1976; Juraska, 1982; Murphy and Magness, 1984; Braitenberg and Schüz, 1991; Bannister and Larkman, 1995; Ishizuka *et al.*, 1995), with appropriately cautious heterospecific comparisons providing valuable insights into the characteristics of cortical neuropil. Unfortunately, there have only been a handful of such studies in non-human primates, and even fewer in humans. Moreover, when analyzing data from human subjects, several special methodological issues constrain potential generalizations (Scheibel, 1988; Flood, 1993; Jacobs *et al.*, 1993b, 1997).

Human subjects. Practical considerations in human research are numerous, including the restrictions of retrospective analyses and the problems of relatively small sample sizes. These are significant obstacles because correlative research on human dendritic systems typically requires the broadest possible sociocultural, vocational, and avocational histories on subjects (Scheibel *et al.*, 1990), and because large sample sizes are required to overcome the tremendous interindividual variation that characterizes human tissue (Ojemann and Whitaker, 1978; Ojemann *et al.*, 1989; Stensaas *et al.*, 1974; Whitaker and Selnes, 1976). Moreover, it is impossible to determine in *post-mortem* tissue whether topographically identical cortical areas in different individuals share the same function. Fortunately, for the purpose of regional comparisons, each subject can serve as his/her own control, insofar as all areas of the cortex have been exposed to the same historical variables.

Histology. Even more limiting in human research are the autolytic consequences of *post-mortem* delays (Williams *et al.*, 1978; de Ruiter, 1983) and the restricted number of histological techniques that can be employed on immersion-fixed tissue. By far the most common stain for human brain tissue is the Golgi silver impregnation technique (see Figure 6.2), the relative merits of which are well documented (Scheibel and Scheibel, 1978; Braak and Braak, 1985). There are, however, innumerable variations of Golgi impregnations, each with its own idiosyncratic characteristics (Buell, 1982; Meller and Dennis, 1990), which further complicate cross-study comparisons. Recently, modern intracellular injection techniques have focused attention on the limitations of such silver impregnation methods. Although fluorescent dyes (e.g. Lucifer Yellow) have proven effective in

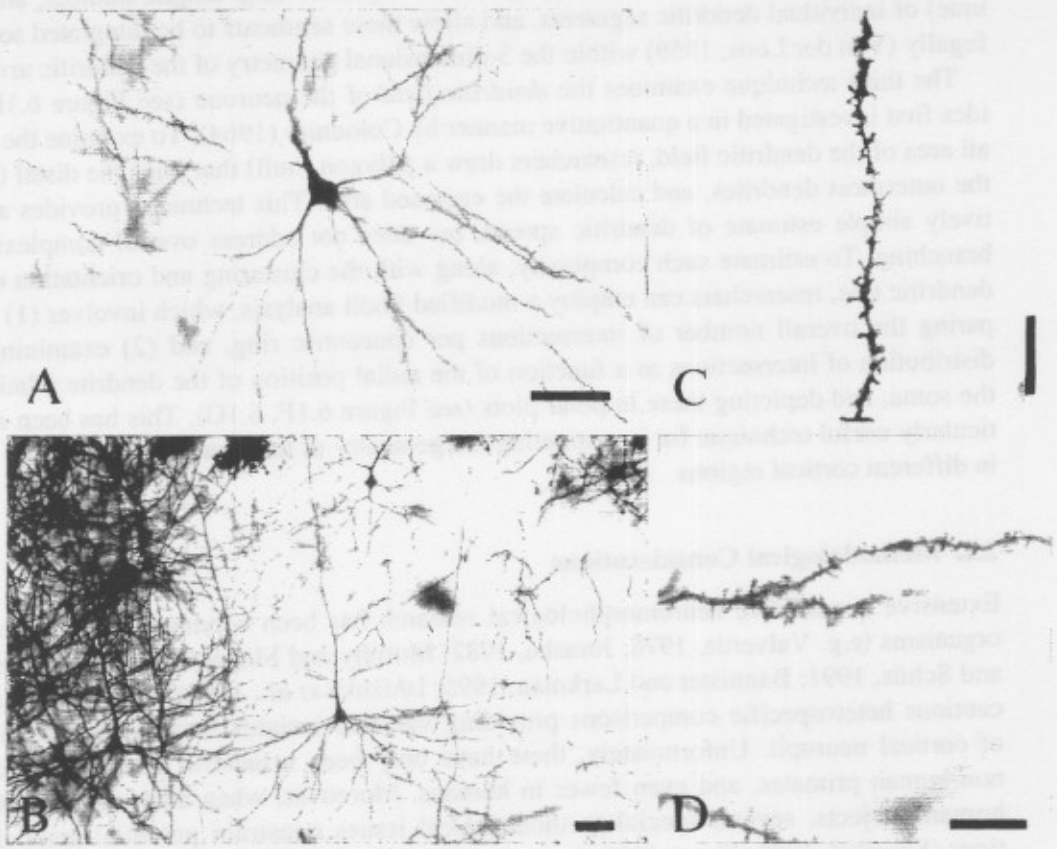

Figure 6.2. Photomicrographs of human supragranular pyramidal cells (**A** and **B**) and associated basal dendritic spines (**C** and **D**) stained with a modified rapid Golgi technique. Several individuals and Brodmann's areas (BA) are represented: **(A)** M32 (=32 year-old male), angular gyrus (BA39); **(B)** M23, prefrontal pole (BA10); **(C)** F15 (=15 year-old female), somatosensory cortex (BA3-1-2); and **(D)** M14, inferior prefrontal pole (BA11). For **A** and **B**, scale bars = 50 µm; for **C** and **D**, scale bars = 10 µm.

neuromorphological reconstructions in non-human animals (Trommald *et al.*, 1995; Elston *et al.*, 1996), they remain somewhat problematic in human autopsy tissue (Ohm and Diekmann, 1994; Belichenko and Dahlström, 1995) due to factors such as dye leakage. Therefore, despite the development of new histological techniques, the Golgi methods remain the stain of choice in extensive quantitative studies of immersion fixed human tissue.

Quantification. Several factors determine what a particular quantitative and histological technique will reveal about cortical neuropil. Here we outline four of these factors. (1) Findings will be substantially affected if separate subpopulations of cells are quantified (e.g. layer II *vs* layer III pyramidal cells), even within the same region (Larkman, 1991; Matsubara *et al.*, 1996). (2) Section thickness, which typically ranges from 50 µm to 200 µm in human Golgi preparations (e.g. Takashima *et al.*, 1981; Koenderink *et al.*, 1994), can also substantially affect quantitative measures by producing varying degrees of cut dendritic segments (Jacobs *et al.*, 1997). (3) Quantitative studies conducted under dry (as opposed to oil-immersion) objectives will result in a diminution of observed length measurements (Uylings *et al.*, 1986). (4) Spine counts, which underestimate actual numbers if they quantify only visible spines, will vary considerably with distance from the soma (Globus and Scheibel, 1967a; Marin-Padilla, 1967), and between the basal and

apical dendrites of pyramidal neurones (Uemura, 1980). Given these constraints, among others, it should be clear that quantitative measurements typically represent relative rather than absolute values, and provide but a small window into the overall arrangement and complexity of cortical neuropil.

3. INDIRECT INDICATORS OF REGIONAL VARIATION IN CORTICAL NEUROPIL

The first quantitative study of cortical dendritic structure appears to have been Bok's (1936) examination of the relationship between the nuclear volume of the cell and the number of dendritic branches. In terms of regional cortical variation, the first quantitative documentation appears to be Sholl's (1953) pioneering exploration of the dendritic branching pattern in cat visual and motor cortices. In addition to finding a positive relationship between overall dendritic length and segment number, Sholl observed a greater number of branches in the visual area compared with the motor area for both pyramidal and stellate cells. Since Sholl's initial observations, however, most quantitative neuromorphological investigations have not directly addressed regional dendritic variation. Instead, they have focused primarily on one cortical area at a time, while exploring factors such as hemispheric differences, cortical development, and aging. Limited inferences related to cortical variation are nevertheless possible when findings from other types of research (e.g. neuroimaging) are integrated.

3.1. Hemispheric Differences

The most general indicator of regional variation involves comparison of homologous areas in the two cerebral hemispheres. Several investigations of this nature have been conducted in humans, particularly on cortical areas involved in language. In an extensive study of the human auditory cortex, Seldon (1981a,b, 1982) found that pyramidal cell basal dendrites exhibited a larger tangential extent in the left hemisphere (LH) than in the right hemisphere (RH). It was postulated that this dendritic advantage was related to greater capacity for differential phonemic responses in the computationally specialized LH. Similarly, slightly more complex basal dendritic systems have been documented in classical Wernicke's area over the RH homologue (Jacobs *et al.*, 1993b). Findings in classical Broca's area have been mixed. Scheibel *et al.*, (1985) found that higher order dendritic segments tended to be more complex in the LH over the RH, presumably because of the complexity of LH speech processing (cf. Jacobs *et al.*, 1993a). In a very limited study, however, Hayes and Lewis (1996) failed to observe interhemispheric differences of dendrites in magnopyramidal neurones in Broca's area, but did suggest that LH cells may be specialized to receive a more restricted complement of afferents. Given that these quantitative morphological observations are consistent with documented interhemispheric functional differences (Walker, 1980; Seldon, 1985; Zatorre *et al.*, 1992), one can suppose with some confidence that quantitative intrahemispheric differences should also obtain across various cortical areas. It should be emphasized, however, that these dendritic systems are extremely plastic. As such, each quantitative study provides but a synchronic "snapshot" of the cortical neuropil, a snapshot that can be diachronically enriched by observations of developmental and aging.

3.2. Development

Dramatic histological changes characterize pre- and post-natal cortical development, including transient overproduction of neuropil, and selective elimination of excessive connectivity (Marin-Padilla, 1970; Rakic *et al.*, 1986; Mrzljak *et al.*, 1990). Several quantitative dendritic investigations have elucidated the timeline in primates for some of these changes in individual cortical areas (Schadé and Van Groenigen, 1961; Schulz *et al.*, 1992; Koenderink *et al.*, 1994; Koenderink and Uylings, 1995) but have not directly suggested regional variability. In their cross-sectional, developmental human study, however, Simonds and Scheibel (1989) inferred a gradual transition in dendritic primacy (i.e. relative complexity of dendritic trees) from the RH to the LH, and from the orofacial motor cortex to the motor speech region, intimating the adult pattern they had previously observed (Scheibel *et al.*, 1985). More recently, the Jacobs laboratory (unpublished data) has compared basal dendritic systems across multiple cortical regions (Brodmann's area, BA 3-1-2, BA4, BA18, and BA10) in human infants and adults. In infants, those regions that mature earliest (BA3-1-2 and BA4) tend to exhibit more complex dendritic trees than those that mature later (BA18, and especially BA10), a finding consistent with the fact that primary cortical areas are initially more active metabolically than association regions (Chugani *et al.*, 1987). In the adult, the regional dendritic pattern tends to be reversed for these four regions; that is, BA10 in the adult surpasses all other regions in dendritic complexity (see below).

These morphological findings, coupled with measures of quantitative synaptogenesis (Huttenlocher and Dabholkar, 1997) and with metabolic indicators (Chugani *et al.*, 1987; Jacobs *et al.*, 1995), indicate a heterochronous path for cortical development. This path is particularly clear in humans, where synaptic density peaks at approximately 3 months postnatally in auditory cortex, at 8–12 months in striate cortex, and after 15 months in frontal cortex (Huttenlocher *et al.*, 1982; Huttenlocher and de Courten, 1987; Huttenlocher and Dabholkar, 1997). Coincident with this synaptic proliferation, local cerebral metabolic rates begin to increase between 1–2 years of age (Chugani *et al.*, 1987). Dendritic growth continues for several more years, even after neuronal and synaptic density decline (Conel, 1939–67; Schadé and Van Groenigen, 1961). With some regional variation, greatest dendritic length in humans is probably reached between 8–10 years of age (Becker *et al.*, 1984; Semenova *et al.*, 1989; Mrzljak *et al.*, 1990; Jacobs and Scheibel, 1993). This dramatic growth in dendritic arborization coincides with a concomitant increase in the brain's metabolic demands (Mata *et al.*, 1980; Nudo and Masterton, 1986). Thus, the metabolic plateau in humans (at about 50% above adult levels) is achieved between 4–9 years of age (Chugani *et al.*, 1987). In terms of regional dendritic variability, the importance of this heterochronous cortical development lies in the finding that some cortical areas in the resting adult brain (e.g. prefrontal cortex) tend to exhibit higher rates of metabolism than other cortical areas (Roland, 1984), in turn suggesting enhanced synaptic activity and greater dendritic complexity in those more active regions.

3.3. Aging

Quantitative dendritic investigations have contributed greatly to our understanding of the aging process. In one of the first (cross-sectional) studies to examine individual segment length by digitizing camera lucida tracings, Cupp and Uemura (1980) suggested that

terminal basal segment growth may continue with age in some neurones in the frontal cortex of rhesus monkeys, although some neurones may exhibit a distoproximal type of degeneration. Neurones in different layers may be particularly susceptible to the aging process. Nakamura *et al.* (1985), for example, noted that layer V basal dendrites appeared to be more affected by the aging process than those in layer III. Using a Sholl analysis in the parahippocampal gyrus, Buell and Coleman (1981) postulated that the normal aging cortex appears to contain both regressing and proliferating (pyramidal) dendritic systems, suggesting continued plasticity in the adult human brain. This age-related cortical plasticity appears wide-spread, insofar as the possibility of these two co-existing populations of neurones has been reconfirmed in subsequent studies on granule cells of the dentate gyrus (Flood *et al.*, 1985) and supragranular pyramidal neurones in Wernicke's area (Jacobs and Scheibel, 1993).

In one of the first studies to examine multiple regions of the human cerebral cortex (specifically, BA4, BA6, BA39, and BA10), Schierhorn (1981) documented age-related decreases in spine density, which appeared to be consistent for all four areas, although specific regional comparisons were not made. The only study to date that has specifically compared age-related changes in dendritic/spine systems across multiple cortical regions is Jacobs *et al.* (1997), which explored supragranular pyramidal neurones in secondary visual (BA18) and prefrontal (BA10) regions in 26 human brains ranging from 14 to 106 years of age. Dendritic measures, particularly for spine systems, decreased substantially from the youngest individuals to approximately 40 years of age, after which the measures remained relatively stable. These losses appeared to be somewhat greater in BA10 than in BA18, which is consistent with other research indicating that certain regions (e.g. frontal lobes, selected association regions) may be particularly susceptible to aging (Kuhl *et al.*, 1982; Terry *et al.*, 1987; Raz *et al.*, 1993, 1997; Sullivan *et al.*, 1995). More extensive quantitative neuromorphological investigations are still required to evaluate age-related regional loss in cortical neuropil (for review, see Coleman and Flood, 1987).

4. DIRECT INVESTIGATIONS OF REGIONAL VARIATION IN CORTICAL NEUROPIL: NON-HUMAN PRIMATES

In recent years, an extensive series of studies by Elston and Rosa on monkey visual pathways has directly addressed the question of regional dendritic variation. Using Lucifer Yellow injection techniques, a modified Sholl analysis, and dendritic field measures, these investigations have examined basal dendritic complexity along the hierarchically arranged occipitotemporal and occipitoparietal visual pathways, and in the frontal eye fields (see Figure 6.3 for a summary).

4.1. The Occipitotemporal Visual Pathway

In one of their earliest comparative studies, Elston *et al.* (1996) examined four areas of the adult Marmoset monkey brain (*Callithrix jacchus*): first (V1) and second (V2) visual areas, the dorsolateral part (DL) and the fundus of the superior temporal (FST) region. They found larger dendritic fields in the pyramidal cells of extrastriate regions, which are involved in shape/color processing (DL) and motion/spatial analyses (FST; Boussaoud *et al.*, 1990), than in primary visual cortical areas (V1, V2) involved in the early stages of visual

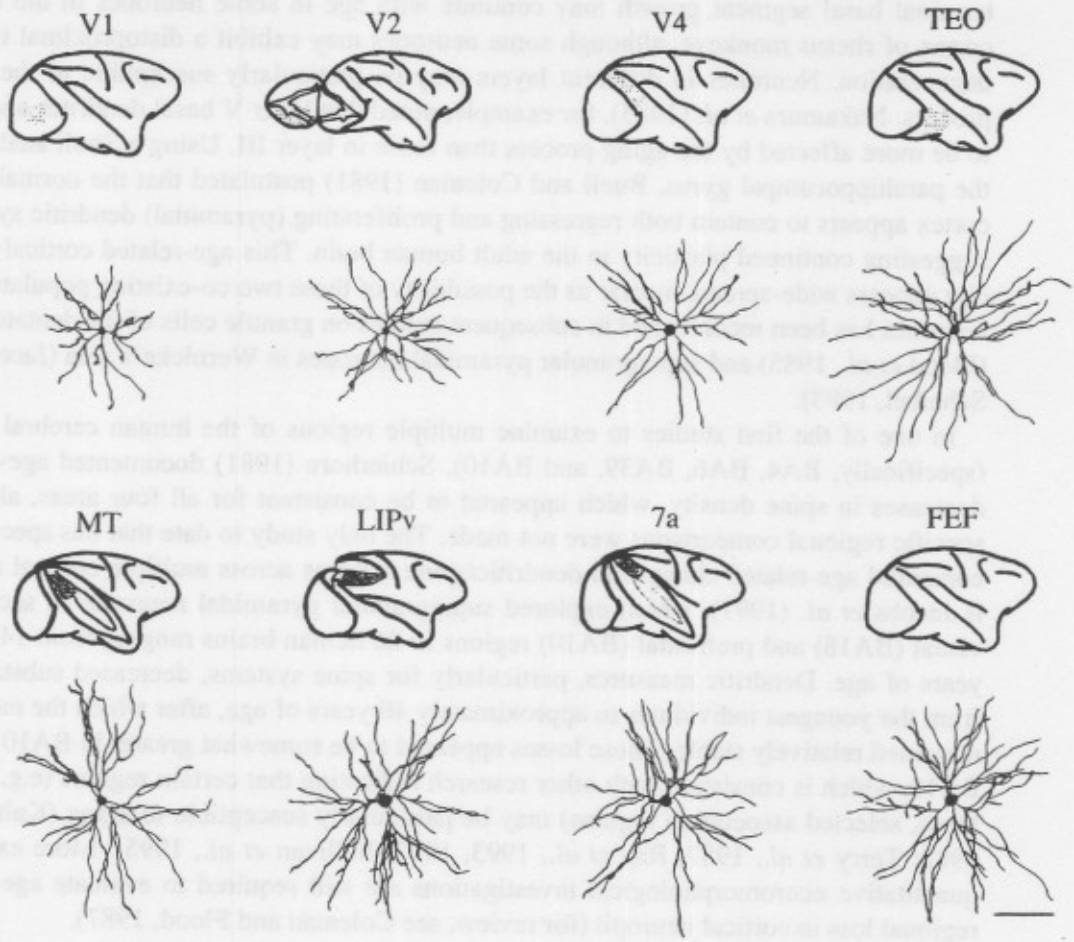

Figure 6.3. Relative position of cortical tissue samples from the monkey, and representative tracings of supragranular pyramidal neurones (synthesized from Elston and Rosa, 1997, 1998a,b). Basal systems are drawn in a plane tangential to the cortical layers and represent neurones in the 60th complexity percentile (scale bar = 100 μm). These areas are arranged in a relative hierarchy, reflecting a general progression in dendritic complexity along the occipitotemporal and occipitoparietal visual pathways, and in the frontal eye fields: primary visual cortex (V1), secondary visual cortex (V2), the fourth visual region (V4), a temporal lobe subdivision (TEO), the middle temporal region (MT), the lateral intraparietal area (LIPv), the anterior bank of the superior temporal sulcus in the parietal lobe (7a), and the frontal eye fields (FEF).

processing. This caudal-rostral progression in field size suggests a more extensive input sampling by dendritic systems at higher levels, and corresponds with demonstrated size increases in intrinsic axonal clusters (Yoshioka *et al.*, 1992; Amir *et al.*, 1993). This is expected insofar as the area of axonal patches appears positively correlated with the basal dendritic field of superficial pyramidal cells along this caudal-rostral visual gradient (Lund *et al.*, 1993).

In a similar, but more extensive investigation of adult *Macaca fascicularis*, Elston and Rosa (1998b) explored the dendritic and spine characteristics of pyramidal neurones in four visual regions: V1, V2, V4, and the occipitotemporal transitional zone (TEO). Several morphological differences were observed both within and across cortical regions. Within V1, cells located in cytochrome oxidase-rich blobs had more extensive dendritic fields than those in interblob regions. Dendritic trees which were morphologically-oriented

(i.e. dendrites clustered in two diametrically opposing directions) and directionally-biased (i.e. dendrites clustered in a particular direction) were more common in V1 and V2 than in more rostral visual areas (V4 and TEO), where non-biased cells predominated. Finally, not only did more rostral, higher visual areas (V4 and TEO) exhibit significantly larger dendritic fields than primary regions (V1 and V2), but the number of spines along the basal dendritic array roughly doubled at each successive stage in the pathway. These findings suggest a stepwise progression in dendritic complexity, with the more rostrally located, spine-dense neurones integrating a wider range of (non-visual) modulatory input than the more caudally located, sparsely-spiny dendritic trees (Moran and Desmond, 1985; Miyashita *et al.*, 1993).

4.2. The Occipitoparietal Visual Pathway and Frontal Eye Fields

By extending their investigations to macaque temporo-parietal lobe visual areas (specifically, the middle temporal area, MT; the lateral intraparietal area, LIPv; and the dorsal superior temporal sulcus, 7a), Elston and Rosa (1997) have provided additional support for a progressive hierarchy, although morphological differences were not as pronounced as those in the occipitotemporal visual pathway. They documented a serial increase in basal dendritic field territories and in branching complexity for pyramidal neurones in the early stages of the occipitoparietal pathway (V1, V2 and MT), but not in the latter stages (MT, LIPv and 7a). As in the occipitotemporal pathway, orientation and directional biases were less marked in more rostral visual areas than in the primary visual regions. Finally, by coupling (visible) spine estimates with basal (but not apical) dendritic extent, they extrapolated a clear stepwise progression in the average spine counts from V1 (799 spines/neurone) to 7a (2572 spines/neurone).

When pyramidal neurones in the two parietal regions (LIPv and 7a) were compared with those in the frontal eye fields (FEF), clear differences emerged, with FEF neurones being more complex in terms of basal dendritic field size and branching complexity (Elston and Rosa, 1998a). Moreover, spine counts in FEF neurones were approximately 30% higher than in the parietal regions. FEF neurones had the largest and most complex basal dendritic systems, with most dense spines, of any of the areas Elston and Rosa had examined, presumably because FEF cells are less functionally compartmentalized, integrating extensive polymodal input (Huerta *et al.*, 1986). Incorporation of FEF neurones into the visual pathways thus reveals an even more general caudal-rostral complexity gradient for basal dendritic systems. Although progression along a proposed hierarchy may not be paralleled exactly by concomitant increases in dendritic field area, especially if functional or anatomical classification within that hierarchy is uncertain, other factors such as spine density and dendritic orientation may contribute significantly to the ultimate structure of hierarchically arranged neuropil.

5. DIRECT INVESTIGATIONS OF REGIONAL VARIATION IN CORTICAL NEUROPIL: HUMANS

Much of the early quantitative work on regional variation in human dendritic systems was performed in the Scheibel laboratory, and was inspired by the observation that certain functional talents (e.g. eidetic imagery) are associated with particular anatomical arrangements

(Scheibel, 1988). In a pioneering undertaking to explore this potential structure-function relationship, Scheibel *et al.* (1990) quantified basal dendritic systems by means of a Sholl analysis in four cortical regions of the LH: somatosensory cortex (BA3-1-2—thoracic region; BA3-1-2—finger region), prefrontal cortex (BA9), and the supramarginal gyrus (BA40). They found partial support for a positive relationship between dendritic extent and functional complexity insofar as the dendritic arbors in the two association cortices (BA9 and BA40) and in the finger region of BA3-1-2 were typically more complex than those in the thoracic region of BA3-1-2 (recall Figure 6.1B).

More recently, Schlaug *et al.* (1993) compared layer V basal dendritic systems in the anterior (BA24b) and posterior (BA23b) cingulate gyrus by means of a Sholl analysis. Consistent with the posterior-anterior gradient suggested by Elston and Rosa's research, the anterior cingulate exhibited greater dendritic complexity than the posterior cingulate. This anterior advantage may reflect functional differences between the two regions as well as differences in interconnectivity (Vogt *et al.*, 1979), with the anterior cingulate pyramidal cells receiving diverse synaptic input of both an affective and a cognitive nature (Devinsky *et al.*, 1995). Importantly, the study also incorporated a quantitative measure that has seldom been examined with regard to dendritic extent: cell packing density. The anterior cingulate region was characterized by a lower cell packing density than the posterior portion, thus indicating an inverse relationship between cell packing density and dendritic arborization, at least in homotypical isocortex. Incorporating both measures in future quantitative morphological research should provide valuable insights into regional distributions of neuropil and interconnectivity patterns.

At present, the most extensive work on regional dendritic variation in humans has been performed in the Jacobs laboratory, which has been exploring the morphological underpinnings of the functional cortical hierarchy proposed by Benson (1993, 1994). Benson's hierarchy draws heavily on the sensory-fugal gradients of cortical connectivity proposed by Mesulam (1985), which have recently undergone considerable elaboration (Mesulam, 1998). In Benson's over-simplified, but useful hierarchical schema, the cerebral cortex is roughly classified into four divisions based on clinical/anatomical correlations: primary, unimodal, heteromodal, and supramodal (see Table 6.1). These cortical types represent progressively more complex levels of neural processing. Although these divisions and their anatomical boundaries are far from absolute, they do provide an initial framework for examining dendritic/spine systems vis-à-vis a functional hierarchy. To date, two studies have been performed within this hierarchical schema to explore regional dendritic variation.

Table 6.1. Proposed functional hierarchy for human cerebral cortex[a]

Cortical divisions	*Function*	*Sample areas*
Primary cortex	Transfer of sensory or motor impulses	BA3-1-2, BA4
Unimodal association cortex	Discrimination, categorization, and integration of single modality information to form a unimodal percept	BA18, BA22, BA44
Heteromodal association cortex	Formation and processing of complex multimodal percepts	BA6B, BA39
Supramodal association cortex	Executive control of cognitive networks	BA10, BA11

Note
[a] Based on Benson (1993, 1994).

The first investigation, mentioned previously with regards to aging (Jacobs *et al.*, 1997), examined dendritic/spine differences between the secondary occipital area (BA18) and the prefrontal cortex (BA10). BA18, which distributes functionally unique streams of visual information (e.g. color, form, orientation) to other extrastriate areas (Burkhalter and Van Essen, 1986; Gegenfurtner *et al.*, 1996), represents typical unimodal cortex. BA10, which is involved in several higher level integrative functions (e.g. drive, executive control, planning; Stuss and Benson, 1984), represents the quintessential supramodal region of the brain. As predicted, the basal dendrites and associated spines of supragranular pyramidal cells in BA10 were significantly more extensive than those in BA18—by approximately 18% for total dendritic length, and by approximately 35% for spine number (recall Figure 6.1D). Reinforcing the robust nature of this finding, this regional advantage for BA10 was observed in all but a few of the 26 individuals examined. Recently, we have also documented that the pyramidal cell packing density in layer III was 24% greater in BA18 than in BA10 (unpublished data), a finding that further supports an inverse relationship between dendritic length and cell packing density in homotypical isocortex (cf. Schlaug *et al.*, 1993). Regardless of cellular density, the more complex dendritic array in BA10 neurones appears to facilitate a broader sampling of afferent information, thereby potentially increasing their integrative capacity. In contrast, the more limited basilar dendritic systems in BA18 neurones may correspond with more discrete sampling of afferent information (i.e. smaller receptive fields; cf. Rosa and Schmid, 1995), as would be characteristic of information processing that is more unimodal than supramodal in nature. These results appear consistent with the anatomical hierarchy proposed by Pandya and Yeterian (1990), and provide initial support at the dendritic level for Benson's functional hierarchy.

The second investigation (Prather *et al.*, 1997; Jacobs *et al.*, 2001) is perhaps the most extensive quantitative neuromorphological study to date. It examined the basal dendritic/spine systems of supragranular pyramidal cells (N = 800) across eight regions of human cerebral cortex. Tissue was removed from the lateral surface of the LH to represent each level of Benson's hierarchical functional schema: *primary cortex* (somatosensory, BA3-1-2; motor, BA4), *unimodal association cortex* (Wernicke's area, BA22; Broca's area, BA44), *heteromodal association cortex* (supplementary motor area, BA6b; angular gyrus, BA39), and *supramodal cortex* (superior frontopolar zone, BA10; inferior frontopolar zone, BA11). Subsequently, primary and unimodal areas were grouped as "lower integrative regions;" heteromodal and supramodal areas were grouped as "higher integrative regions."

Despite the considerable interindividual variation that typifies human tissue, there were significant differences across Brodmann's areas and between the higher and lower integrative zones for all dendritic and spine measures (see Figure 6.4). Dendritic systems in primary and unimodal regions were consistently less complex than heteromodal and supramodal areas. Nevertheless, the exact sequence of individual Brodmann's areas depended somewhat on what aspect of the dendritic tree was examined (e.g. total dendritic length: BA3-1-2 < BA22 < BA4 < BA44 < BA11 < BA39 < BA6b < BA10; spine number: BA3-1-2 < BA22 < BA4 < BA44 < BA6b < BA11 < BA39 < BA10). The range within these rankings is substantial, with total dendritic length in BA10 being 31% greater than that in BA3-1-2, and dendritic spine number being 69% greater.

In terms of individual areas, it is not surprising that BA6b, BA10, and BA39 exhibited the most elaborate dendritic systems given the vast interconnections and functional

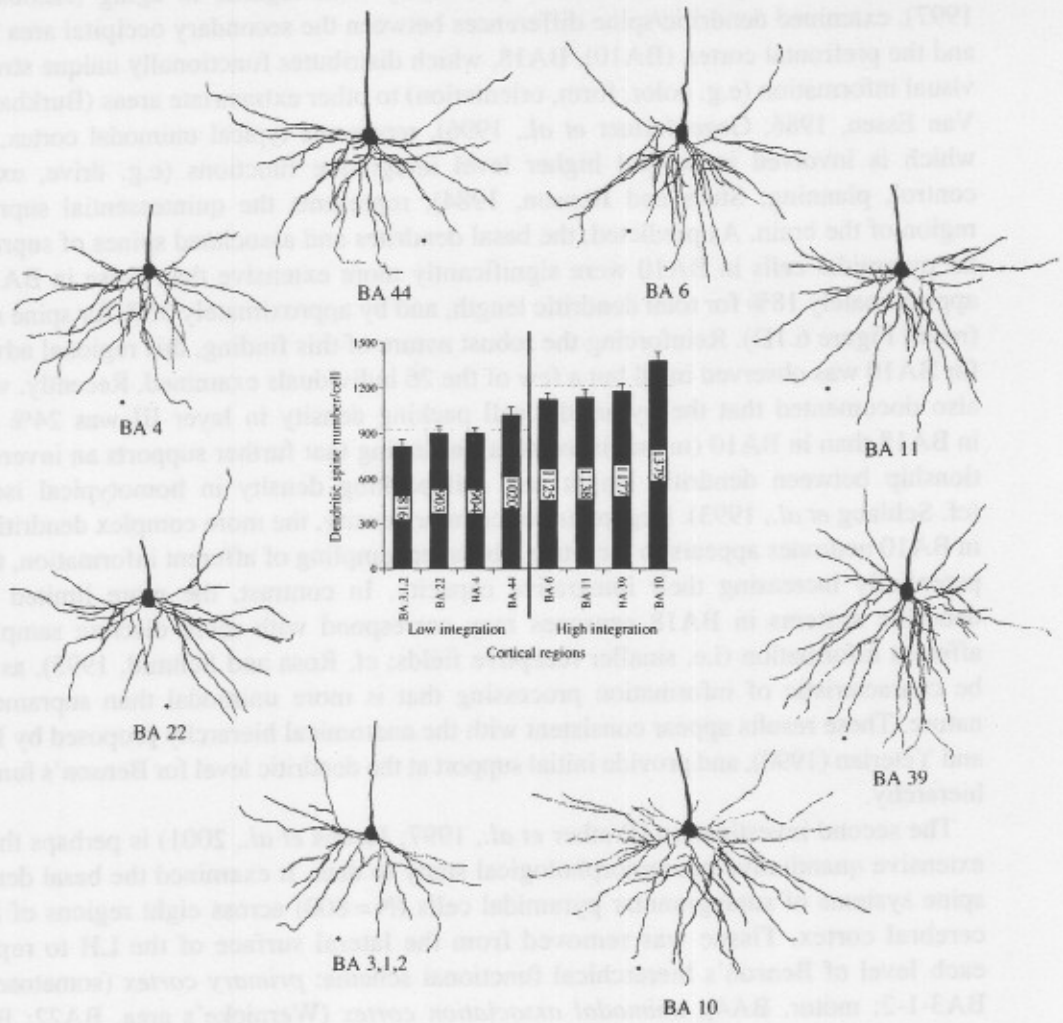

Figure 6.4. Sample tracings of human supragranular pyramidal cells and a bar graph of the dendritic spine number (DSN) for eight Brodmann areas (BA), arranged from lowest (BA3-1-2) to highest (BA10) in terms of overall complexity. Areas have also been grouped as Low (BA3-1-2, BA22, BA4 and BA44) and High (BA6, BA11, BA39 and BA10) Integration regions, with the average DSN value for each grouping indicated by the dotted lines. Note that DSN values represent only spines that were visible on the basal dendrites. In general, DSN values in the High Integration regions are considerably higher than those in the Low Integration regions. This hierarchy is roughly reflected in the individual tracings of neurones (synthesized from Prather *et al.*, 1997; Jacobs *et al.*, 2001). Scale bars = 100 µm.

complexity of these cortical regions (for reviews, see Goldberg, 1985; Zilles, 1990; Roland, 1993). It is unclear why the dendritic arbors of BA22 were at the low end of the spectrum, although this may be due to this area's close proximity to the primary auditory cortex (see Jacobs and Scheibel, 1993). Conceivably, a section more posterior along the superior temporal gyrus would be involved in synthesizing a greater proportion of polymodal information, especially given that the sensory speech region receives a wide sampling of cortical and subcortical input (Pandya *et al.*, 1969; Jones and Powell, 1970; Seldon, 1985). Thus, in some instances, there were minor exceptions to Benson's functional hierarchy (e.g. a primary area such as BA4 being slightly more complex than a predominantly—though probably not exclusively—unimodal area such as BA22). Such exceptions should

be expected, given the vast interconnectivity of cortical areas, which do not readily conform to strict hierarchical boundaries. On the whole, however, the results indicate that the dendritic/spine systems of cortical areas involved in the initial stages of information processing are not as complex as those involved later in the processing stream, and further underscore that the processing demands placed on dendritic systems in various cortical regions substantially influence their ultimate expression (Cajal, 1894; Hebb, 1949; Diamond *et al.*, 1964).

6. DENDRITIC INTEGRATION AND FUNCTIONAL IMPLICATIONS

Functional localization in the cerebral cortex has become one of the conceptual foundations of neuroscience. It has traditionally been based on two streams of research activity: (1) clinical and physiological dissections (e.g. Broca, 1861; Fritsch and Hitzig, 1870; Woolsey, 1958), which established areal specificity for the various aspects of perception and behaviour at a cortical level, and (2) cytoarchitectonic studies, which began to define the anatomical extent and organization of such areas (e.g. Brodmann, 1909; Von Economo, 1929). At the same time, the beginnings of studies at higher resolution, based on visualization of dendritic ensembles and axonal patterns, became possible with the use of the Golgi silver impregnation methods (Golgi, 1886; Cajal, 1909; Lorente de Nó, 1922). However, useful anatomical comparisons of cell structure and neuropil patterns across areas have only become possible with the development of quantitative morphological techniques (e.g. Bok, 1936; Sholl, 1953). A sufficient number of such analyses now suggests that some patterns in neuropil may eventually be understood in terms of the nature of the cortical function subsumed.

One such pattern appears to be the length and complexity of dendrite arrangements. We had previously suggested a positive correlation between computational complexity and dendritic extent (Scheibel *et al.*, 1985). Recently, several studies have provided more rigorous support for this idea (Elston and Rosa, 1998b; Jacobs *et al.*, 2001), which correlates reasonably well with hierarchical conceptions of cortical organization. Essentially, as one progresses from "first level" cortical input stages through intermediate levels of association areas (unimodal and heteromodal) to the presumed hierarchically highest levels of cortical associative activity (supramodal), there is a coincidental increment in basal dendrite length and spine number. As indicated above, the increase in dendrite length in humans over the entire sequence is of the order of one third, and that of total spine number by about two thirds. Although fairly consistent, and significant in a quantitative sense, these are by no means massive changes. On an entirely intuitive level, it might be difficult to conceive that the robust *qualitative* differences assumed to exist between processing mechanisms active in BA18 and BA10, for instance, can in large part be accounted for by a 30% difference in dendritic extension. Certainly, factors other than dendrite extent must be responsible for the dramatic inter-areal differences in function.

Phrasing the question differently, we might wonder whether the relatively modest though consistent differences in basal dendrite dimensions among the cortical areas studied are minor variants on a standard pattern, thereby providing only processing changes of a quantitative nature, or whether these differences reflect much more fundamental computational mechanisms, thereby providing variations of a qualitative nature. Studies by Tyc-Dumont and colleagues suggest that the latter may be true (Gogan and

Tyc-Dumont, 1989). In a series of communications, these researchers report significant differences in the behaviour of individual dendrites. Each dendrite seems to have its own electrical characteristics depending on a group of parameters, including input resistance, voltage attenuation, and charge transfer effectiveness ratio (Gogan and Tyc-Dumont, 1989). These factors are computed for every dendritic site in the arborization to give the electrical image of the tree.

Structural studies have emphasized the functional importance of the small caliber outermost branches of basal dendrite systems. In the enrichment paradigm, for example, it is these peripheral processes in rats which develop in response to enhanced input and which disappear when the animal is input-deprived (Connor *et al.*, 1981). Similarly in the human brain, it is the development of these smallest caliber (fifth and sixth order) branches in Broca's area of the left hemisphere that accompanies the development and maturation of the language faculty (Simonds and Scheibel, 1989).

Some years ago, on the basis of a group of selective lesion experiments in rabbits, Globus and Scheibel (1967a,b,c) emphasized the essentially modular nature of the dendritic domains of cortical pyramids. For any one cortical area, there was a high degree of consonance in the extent of the horizontal dendritic components (basal and oblique branches and the apical arch). Depending on the location of the cell body, however, the apical shaft might be as short as 100 µm (layer II), or as long as 4000 µm (deep layer V). Fibre terminals of intracortical derivation seemed almost exclusively related to the horizontal branch systems of the cell (i.e. apical obliques and basal dendrites), whereas extracortically derived afferents appeared to terminate predominantly on apical shafts. The extent of the horizontal dendritic component of the cell could then be considered a measure of its exposure to intracortically derived information, especially since the neocortex communicates predominantly with itself (Braitenberg, 1978; Nieuwenhuys, 1994). Progressive increase in the extent of the basal dendritic skirt might therefore be expected to increase the exposure of the neurone to intracortical influences, a correlation that intuitively meets assumptions about the needs of increasingly more complex associative functions.

There have been suggestions that the fine, tapering, outermost branches of the dendritic ensemble may assume a physiological importance out of proportion to the modest fraction of the neuronal dendrite that they represent:

> "Most distally from the soma, the extremely fine dendritic branches are practically independent subunits where nonlinear synaptic interactions operate, and only the results of these operations are transmitted to the soma with different efficiencies, depending on the cable properties of the individual dendritic channel. [Thus] each neuron is like a complex computer with many nonlinear coprocessors operating in parallel." (Gogan and Tyc-Dumont, 1989, p. 129)

It is interesting to recall that earlier physiological studies of neurones led some to the conclusion that, in the case of motoneurones at least, electrotonic considerations indicated that distal dendrites contribute little to electrical events at the soma (Eccles, 1964). On the basis of theoretical considerations, however, Rall (1974) suggested that remote dendrite terminals might exercise significant electrical effects at the cell body. A number of possible mechanisms for this have been advanced over the last thirty years. Among these possibilities, Redman (1973) suggested that more current may be injected by distal

synapses than by proximal ones, thereby resulting in excitatory postsynaptic potentials of approximately similar shape and size at the cell body.

An alternative suggestion by Rall (1974) is based on the observation that the stems of dendritic spines are generally longest and thinnest at the peripheral portions of dendrites and become increasingly short and stubby as the soma is approached (Jones and Powell, 1969). The long thin spine stem has a much higher resistance value and therefore a lower current carrying capacity. Rall suggested that this attenuated spine stem might have value as an impedance matching device vis-à-vis the underlying dendritic branch input. These most peripheral spines might therefore be particularly effective in adjusting synaptic potency:

> "The design principle involved here is to sacrifice maximum power in order to gain flexibility and control. Adjustability of potency means either increase or decrease relative to other synapses. Thus we think of delicate adjustments of the relative weights (potency) of many different synapses to any given neurone. We think of these changes as responsible for changes in dynamic patterns of activity in assemblies of neurones organized with convergent and divergent connective overlaps." (Rall, 1974, p. 17)

Indeed, recent research suggests that the excitability of an entire dendrite may be regulated by changes in distal spine density (Jaslove, 1992). It thus seems likely that synaptic activity in the outermost segments of the dendrite tree not only affects neuronal activity, but may, in fact, exert effects out of proportion to dendritic extent and geographic distance from the soma.

Another aspect of terminal dendrite function that may enrich the role of this portion of the dendrite tree is the possibility of interaction among dendrite terminal branches. In addition to dendro-dendritic synapses such as those described in the olfactory bulb (Rall *et al.*, 1966), a number of investigators have described the presence of dendrite bundles in many sites throughout the central nervous system including the cerebral cortex (Fleischhauer, 1974; Scheibel and Scheibel, 1970). Although the role of such structural complexes has never been fully clarified, it has been suggested that distal dendrites in close apposition to those from other neurones may in fact transmit information, thereby emphasizing again the possibly special role of this portion of the nerve cell (Bras *et al.*, 1987; Gogan and Tyc-Dumont, 1989).

Finally, complementing Rall's theoretical speculations are more recent insights into the active characteristics of dendritic branches provided by high-speed fluorescence imaging and dendritic patch clamping. It seems relatively clear that dendrites can no longer be viewed as simply passive structures adhering to the principles of cable theory (for review, see Johnston *et al.*, 1996). Indeed, at least some cortical dendrites appear capable of sustaining active propagation of electrical potentials through voltage-sensitive Na^+ and Ca^{2+} channels. These active characteristics would indeed boost the effect of distal synaptic input, contributing significantly to synaptic integration locally and across the entire neuron.

7. CONCLUSION

Quantitative neuromorphological techniques have substantially enhanced our understanding of the dendritic ensembles first described and categorized according to qualitative

observations (e.g. Ramón-Moliner, 1962). Indeed, as noted by Sholl (1953), the characteristic dendritic patterns across various cortical regions can only be revealed through quantitative investigations. We conclude this chapter by noting that there is a very strong likelihood that these inter-areal variations in basal dendritic dimensions revealed by quantitative neuromorphological investigations of the cerebral cortex reflect significant differences in the nature of cortical processing. Many other factors are undoubtedly involved in determining the range of computational strategems as one moves from first level sensory representations to the highest associational levels. Some of these are considered elsewhere in this volume. Nonetheless, the characteristics of the receptive dendritic membrane of individual neuronal elements and their variations along the length of the dendritic shaft are bound to represent central issues in our developing knowledge of cortical computation.

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