Cortex, Cognition and the Cell: New Insights into the Pyramidal Neuron and Prefrontal Function

Guy N. Elston

Vision, Touch and Hearing Research Centre, Department of Physiology and Pharmacology, School of Biomedical Sciences, The University of Queensland, Brisbane 4072, Australia

Arguably the most complex cortical functions are seated in human cognition, the how and why of which have been debated for centuries by theologians, philosophers and scientists alike. In his best-selling book, *An Astonishing Hypothesis: A Scientific Search for the Soul*, Francis Crick refined the view that these qualities are determined solely by cortical cells and circuitry. Put simply, cognition is nothing more, or less, than a biological function. Accepting this to be the case, it should be possible to identify the mechanisms that subserve cognitive processing. Since the pioneering studies of Lorent de Nó and Hebb, and the more recent studies of Fuster, Miller and Goldman-Rakic, to mention but a few, much attention has been focused on the role of persistent neural activity in cognitive processes. Application of modern technologies and modelling techniques has led to new hypotheses about the mechanisms of persistent activity. Here I focus on how regional variations in the pyramidal cell phenotype may determine the complexity of cortical circuitry and, in turn, influence neural activity. Data obtained from thousands of individually injected pyramidal cells in sensory, motor, association and executive cortex reveal marked differences in the numbers of putative excitatory inputs received by these cells. Pyramidal cells in prefrontal cortex have, on average, up to 23 times more dendritic spines than those in the primary visual area. I propose that without these specializations in the structure of pyramidal cells, and the circuits they form, human cognitive processing would not have evolved to its present state. I also present data from both New World and Old World monkeys that show varying degrees of complexity in the pyramidal cell phenotype in their prefrontal cortices, suggesting that cortical circuitry and, thus, cognitive styles are evolving independently in different species.

Historical Overview

The Misnomer of Cortical Uniformity

It is perhaps not surprising that many of the pioneers in comparative neuroscience were impressed by the similarity of the cerebral cortex in mammalian species. Their early studies revealed that the cerebral cortex is composed of the same basic neuronal types, often organized into a similar basic laminar pattern. The importance of these findings justified the emphasis placed upon them, and they were instrumental in shaping our present understanding of the structure, development, function and evolution of the cerebral cortex. However, unfortunately, 'similar' was interpreted by many to imply 'same'. As a result it became widely accepted during the latter part of the last century that the cerebral cortex is uniform in structure, the whole of cortex (with the exception of the primary visual area) being composed of the same basic repeated unit (Creutzfeldt, 1977; Mountcastle, 1978; Szentagothai, 1978; Rockel *et al.*, 1980; Eccles, 1984; Douglas *et al.*, 1989; Hendry and Calkins, 1998). Taken to its extreme, this interpretation suggested that any deviation from the basic cortical unit must be erroneous (Szentagothai, 1978). Moreover, many assumed that cortical circuitry is the same in different species (Krubitzer, 1995; Kolb and Tees, 2000; Jerison, 2001). In keeping with this dogma, regional differences in cortical function such as vision, somatosensation and hearing, were attributed solely to the source of their inputs. However, if circuitry in prefrontal cortex, the region of the brain often implicated in cognitive processing, is the same as that in any other cortical region, how could it perform such a complex function as human mentation?

A study of the literature reveals an alternative viewpoint, that is, that the cerebral cortex is characterized by regional and species variations in structure. Although these observations have been ignored by many, some of the pioneering comparative neuroscientists were keenly aware of the functional implications of these regional variations in cortical circuitry. Quoting directly from Santiago Ramón y Cajal's observations:

> En los ratones las prolongaciones basilares son cortas y poco ramificadas, en el hombre se hacen mas numerosas, largas y ramificadas. Ademas las colaterales nerviosas del raton, el mismo que las del conejo, etc, se dicotomizan solomente uno o dos veces, mientras que en el hombre estas mismas colaterales son mas numerosas y se dividen cuatro y cinco veces, constituyendo ramitas tan largas que no se pueden obtener enteras en un sole corte. (Ramon y Cajal, 1894a,b)

> In mice the basal dendrites [of pyramidal cells] are short and have few branches, in man they [the basal dendrites] are numerous, long and highly branched. In addition, the nerve collaterals in mice, as in rabbits etc., divide only once or twice, while in man the same collaterals are more numerous and divide four or five times, making branches so long that the entire branch can never be seen in a single section.

> La pirámide ó corpúsculo psíquico posee caracteres especificos que no faltan jamas . . . la presencia de un tallo y penancho protoplasmático, dirigido hacia al superficie cerebral; la existencia de espinas colaterales en las ramas protoplasmáticas . . . puesto que conforme se asciende en la serie animal, el corpúsculo psíquico se engrandece y complica, es natural atribuir a esta progresiva complicación morfológica, una parte al menos de su progresiva dignidad functional . . . puede, pues, estimarse como verosimil que la célula psíquica desempeña más amplia y últimamemte su actividad cuanto mayor número de expansiones protoplasmáticas, someaticas y colaterales ofrece, y cuanto mas copiosas, largas y ramificadas son las colaterales emergentes de su cilindro-eje. (Ramon y Cajal, 1893)

> The pyramidal cell, or psychic cell, possesses specific characteristics that are never absent . . . a dendritic shaft and tuft directed toward the cerebral surface; the existence of collateral spines on the dendritic processes . . . as one ascends the animal scale the psychic cell becomes larger and more complex; it's natural to attribute this progressive morphological complexity, in part at least, to its progressive functional state . . . it can thus be consid-

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ered probable that the psychic cell performs its activity more amply and usefully the larger the number of somatic and collateral dendrites that it offers and the more numerous, long and branched the collaterals emitted by its axon.

See DeFelipe and Jones (1988) for a translation of Ramon y Cajal's works.

Ramon y Cajal was not alone in documenting regional and species variation in cortical circuitry. Brodmann, von Economo, von Bonin, Walker, the Vogts and Hassler, to mention but a few, were all united in their thinking that different regions of the cortex are composed of different and distinguishable structures (Fig. 1). The extent of regional differences in cortical structures in the brain was investigated in painstaking detail by Conel (1941, 1947, 1955, 1959, 1963, 1967) who published a multiple volume series in which he quantified variation in cell structure in a multitude of cortical areas in the developing human cerebral cortex. Over 250 drawings reveal incredible diversity in pyramidal cell structure (Fig. 2). However, the functional importance of regional variation in cortical circuitry is still ignored by many. The irony is that, while particular cortical areas such as the primary visual area or the primary somatosensory area have become the focus of intensive research because they are *uniquely* identifiable, findings on the structure and function of these cortical areas, in many cases, continue to be generalized across all cortex.

New Vistas on Regional Specialization in Cortical Circuitry

Various groups are now making a combined effort to readdress the issue of regional specialization in cortical circuitry. Recently developed methodologies have allowed the study of new aspects of circuitry, and comparative studies are becoming more common. In particular, new markers such as SMI32 and the calcium-binding proteins parvalbumin, calbindin and calretinin, as well as specific antibodies to receptor subunits, have been brought to the task (for reviews, see Zilles and Clarke, 1997; Morrison *et al.*, 1998; Hof *et al.*, 1999; Preuss, 2001; DeFelipe, 2002). Detailed studies of patterns of axonal projections also reveal impressive heterogeneity in the cerebral cortex (for reviews, see Levitt *et al.*, 1984; Jones, 1986; Goldman-Rakic, 1987; Pandya and Barnes, 1987; Cavada *et al.*, 1997; Rockland, 1997; Geyer *et al.*, 2000). Here, I focus on how the pyramidal cell phenotype in prefrontal cortex differs from that in other cortical regions and the implications of these specializations for cognitive processing. By way of an introduction, I first outline the relationship between structure and function in the most extensively studied of cortical regions, sensory cortex. For it is based on the compelling correlation between circuit structure and function in sensory cortex that we have embarked on an exploration of the role of circuit specialization in prefrontal cortex.

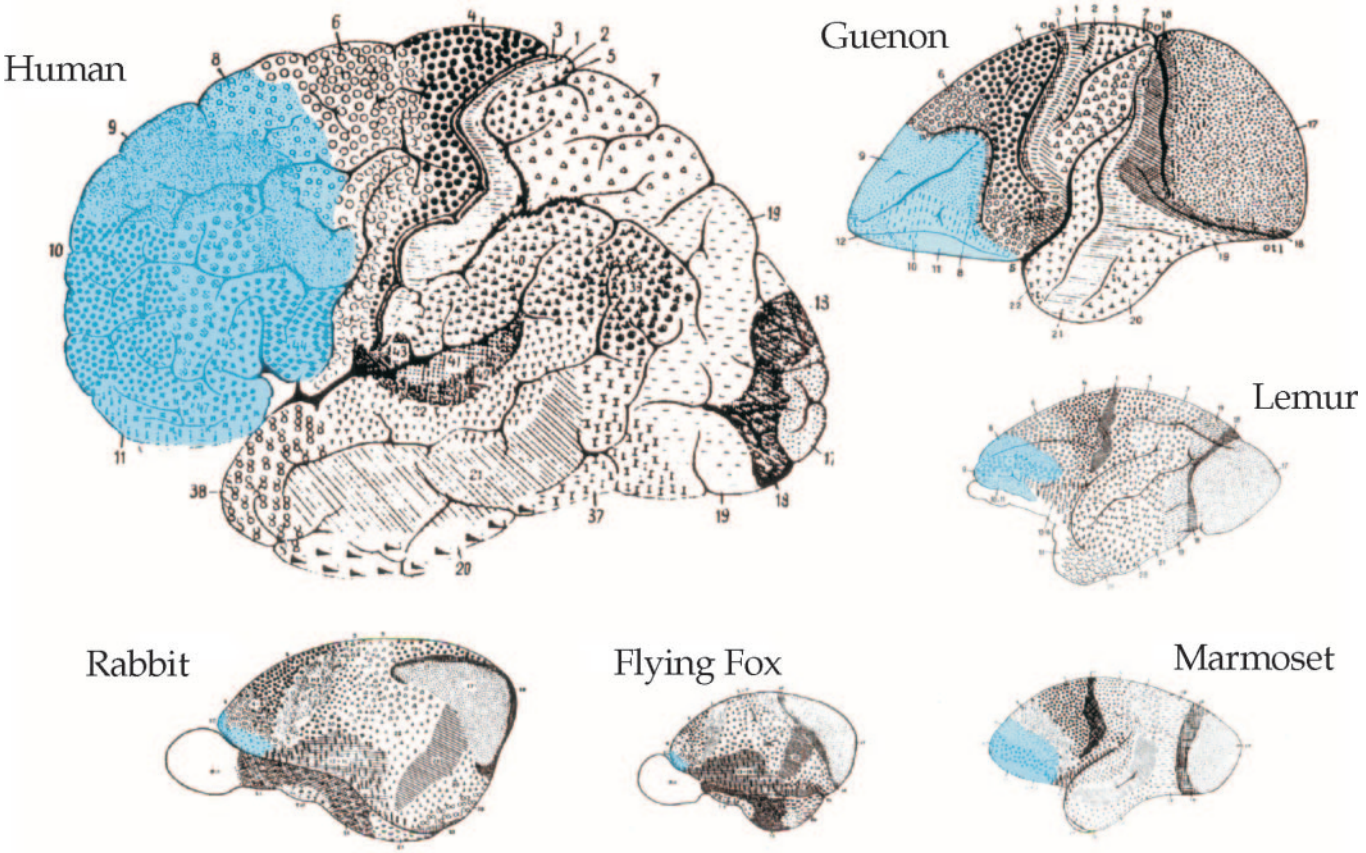


Figure 1. Schematics illustrating relative differences in cortical organization in selected mammalian species, modified from Garey's (1994) translation of Brodmann's (1909) work. In humans, granular prefrontal cortex (blue) occupies 29% of the total cortex, considerably more than in the guenon (11.1%), lemur (8.3%), marmoset (8.9%), flying fox (2.3%) and rabbit (2.2%) (Brodmann, 1913).

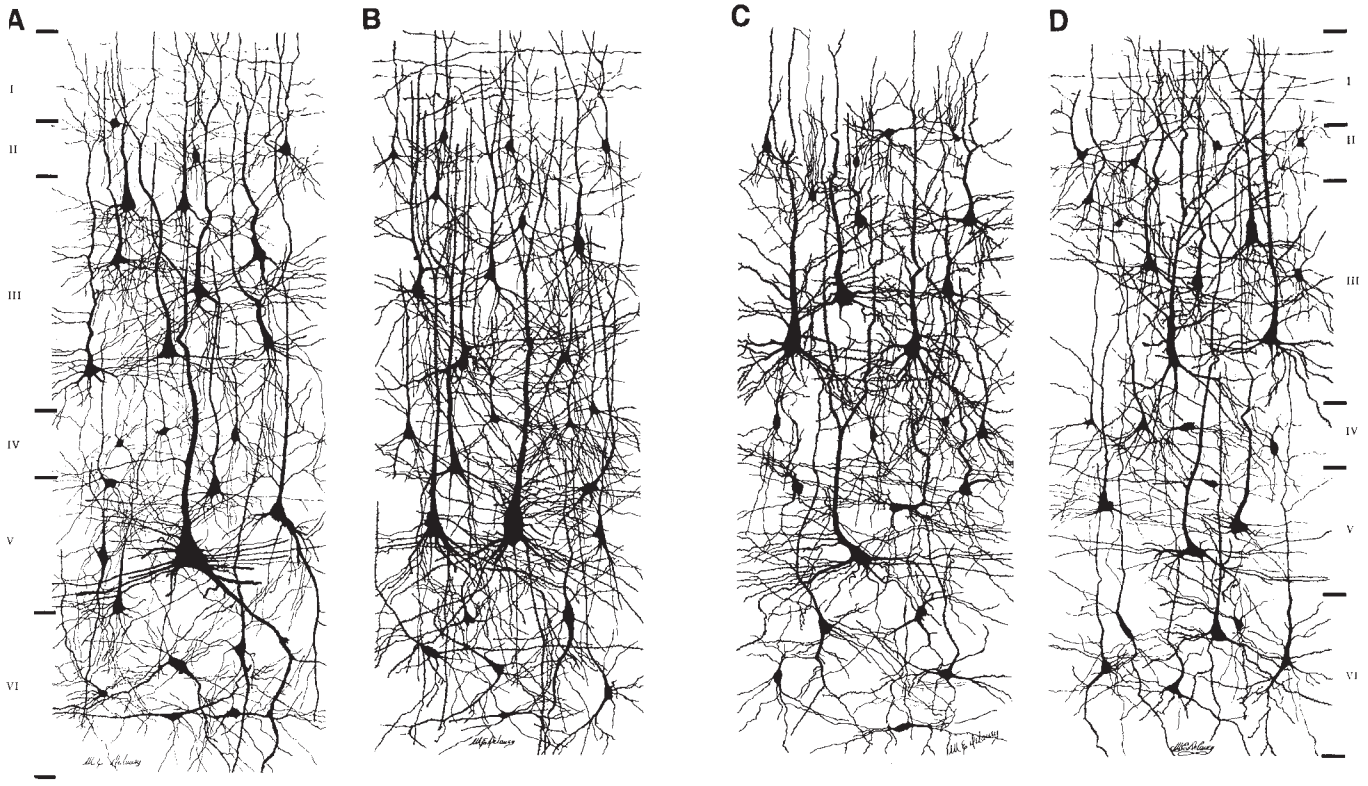


Figure 2. Drawings of cortical neurons in (*A*) the crown of lobulus paracentralis, (*B*) the posterior wall of gyrus centralis anterior, (*C*) the crown of gyrus frontalis superior and (*D*) the anterior wall of gyrus centralis posterior, highlighting interareal differences in pyramidal cell structure in the human brain (modified from Conel, 1959).

Lessons from Sensory Cortex

Of all cortical regions in the brain, the most extensively studied is sensory cortex. In particular, the visual cortex of the macaque monkey has been the focus of much interest due to its parallels with the human visual system (Kaas, 1992). Visual cortex, like other sensory cortices, lends itself to the study of cortical function as specific stimuli can be used to measure specific cellular responses: both the cue and the response can be quantified and correlated.

Monkeys reportedly have as many as 30 cortical visual areas (Felleman and Van Essen, 1991) (Fig. 3), within which neurons process different aspects of vision (e.g. movement, contrast and spectral processing), the outcome of which is a conscious visual percept of the external world (for reviews, see Ungerleider and Mishkin, 1982; Livingstone and Hubel, 1984; Allman *et al.*, 1985; Crick and Koch, 1990; Felleman and Van Essen, 1991; Gross *et al.*, 1993; Singer and Gray, 1995; Cavada *et al.*, 1997; Kaas, 1997; Logothetis, 1998; Zeki, 2001). Recently, significant and systematic differences have been reported in the structure of pyramidal cells in these visual areas (Lund *et al.*, 1993; Elston *et al.*, 1996, 1999a–c, 2001; Elston and Rosa, 1997, 1998a,b, 2000; Elston, 2000, 2003a; Elston and Jelinek, 2001; Jacobs *et al.*, 2001) (Fig. 3). The magnitude and systematic nature of these regional variations in pyramidal cell structure and their consistency across species make it implausible that they might be 'accidental', as suggested by Szentagothai (1978). Here, I will outline briefly how the structural differences in cortical circuitry in different visual areas influence neural and systems functions (for reviews, see Jacobs and Scheibel, 2002; Elston, 2003b,c).

On the Relationship between Structure and Function in Sensory Cortex

Cellular Level

Many aspects of dendritic arbour structure can be identified that may influence neuronal function (for reviews, see Koch, 1999; Koch and Segev, 2001). Three of these features – size, branching pattern and number/distribution of inputs – are considered here. Pyramidal cells characterized by a large dendritic arbour extend over a wider region of cortex than cells with smaller arbours. In macaque visual cortex, the differences in arbour size, coupled with receptive field map compression, result in a >100-fold difference in the region of the visual map sampled by individual pyramidal cells in the primary visual area (V1) and cytoarchitectonic area TEO (Elston and Rosa, 1998a). The proportion of the visuotopic map sampled by pyramidal cells is further increased by patterns of intrinsic neuronal connectivity – i.e. the lattice of horizontal intrinsic axonal patches in visual cortex (Rockland and Lund, 1982, 1983; Rockland *et al.*, 1982; Livingstone and Hubel, 1984; Rockland, 1985; Lund *et al.*, 1993; Fujita and Fujita, 1996) – which are successively more widespread in V1, the second visual area (V2), the fourth visual area (V4) and cytoarchitectonic area TEO. The geometrical relationship between the size of pyramidal cell dendritic arbours and the topography of the intrinsic horizontal lattice of projections reportedly influences their sampling geometry (Lund *et al.*, 1993) and mixing of inputs from multiple sources (for reviews, see Malach, 1994; Elston, 2003b,c).

Differences in the dendritic branching patterns may determine the degree to which the integration of inputs is compart-

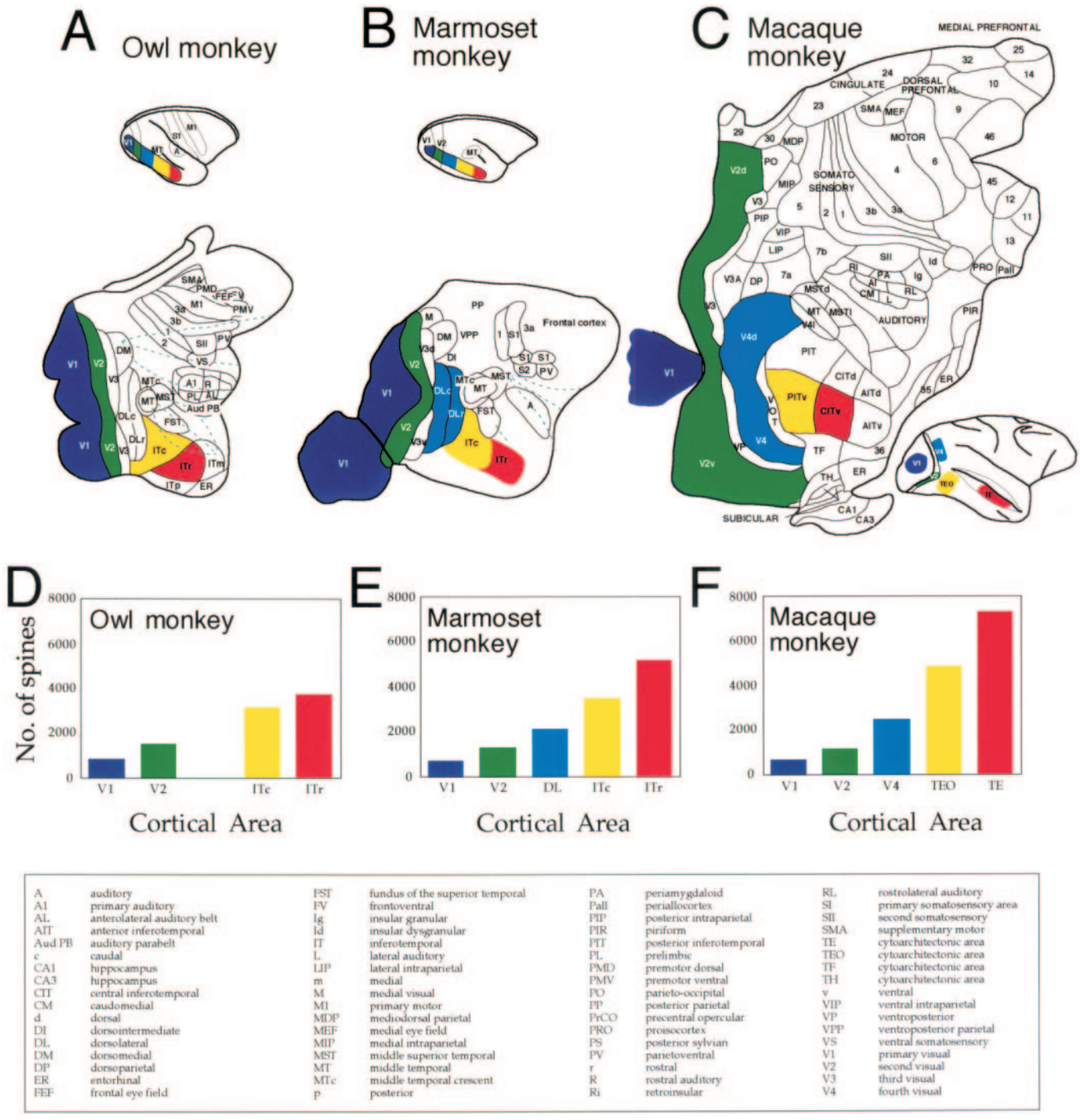
Table 1
Relative proportion of cortical volume occupied by granular prefrontal and precentral cortex in a number of different species (from Brodmann, 1913)

	Species	Total cortical volume (mm^3)	Granular prefrontal cortex (PFC)	Agranular precentral cortex	PFC + agranular precentral cortex (frontal lobe)
Strepsirhini	Man	108 221	30 254 = **27.9**	6117 = 5.7	36 371 = 33.6
	Man	135 470	39 287 = **29.0**	9833 = 7.3	49 120 = 36.3
	Chimpanzee	39 572	6719 = **16.9**	5389 = 13.6	12 108 = 30.5
	Gibbon (*Hylobates*)	16 301	1839 = **11.3**	1651 = 10.1	3490 = 20.4
	Mandrill (*Cynocephalus*)	31 321	2186 = **10.1**	2194 = 10.3	4362 = 20.4
	Baboon (*P. hamadryas*)	20 594	1967 = **9.5**	2898 = 14.1	4865 = 23.6
	Baboon (*P. cynocephalus*)	20 376	2111 = **10.3**	2200 = 10.8	4311 = 21.1
	Macaque	15 308	1733 = **11.3**	1817 = 11.9	3550 = 23.2
	Guenon (*Cercopithecus*)	14 641	1625 = **11.1**	1976 = 13.5	3601 = 24.6
	Capuchin	13 682	1260 = **9.2**	1822 = 13.3	3082 = 22.5
	Marmoset	1649	148 = **8.9**	167 = 10.1	315 = 19.0
Haplorhini	Black lemur	4054	337 = **8.3**	453 = 11.2	790 = 19.5
	Microcebus (*Cheirogaleus*)	921	70 = **7.2**	94 = 10.2	164 = 17.8
	Flying fox[a]	1097	26 = **2.3**	73 = 6.6	99 = 8.9
Carnivores	Dog (*Canis*)	9527	657 = **6.9**	1283 = 13.4	1940 = 20.3
	Cat (*Felis*)	4474	152 = **3.4**	412 = 9.2	564 = 12.6
Lagomorpha[a]	Rabbit (*Lepus*)	1627	36 = **2.2**	148 = 9.1	184 = 11.3
Insectivore	Hedgehog (*Erinaceus*)	575	0 = **0**	24 = 4.0	24 = 4.0
Edentate	Armadillo (*Dasypus*)	2010	0 = **0**	93 = 4.6	93 = 4.6
Marsupial	Opossum (*Didelphys*)	804	0 = **0**	51 = 6.3	51 = 6.3

[a]Included as a primate in the original table (for a review, see Pettigrew *et al.*, 1989).
[b]Labelled as a rodent in the original table.

mentalized within their arbours (Koch *et al.*, 1982; Koch, 1999). The functional outcome of such dendritic processing has been demonstrated in the retina (Taylor *et al.*, 2000) and auditory brainstem (Agmon-Snir *et al.*, 1998). Thus, in visual cortex, the potential for compartmentalization of processing within the highly branched dendritic arbour of cells in the superior temporal polysensory area (STP), a polymodal association area, is greater than that in other cortical areas such as V1 and V2. Modelling studies have shown that the greater potential for compartmentalization results in a significant increase in the representational power of the cell and a greater capacity for learning and memory (Poirazi and Mel, 2001) (Fig. 4). Marked differences in the density of dendritic spines, each of which receives at least one asymmetrical synapse (Colonnier, 1968; Jones, 1968; Peters and Kaiserman-Abramof, 1969), the presynaptic terminals of which contain the excitatory neurotransmitter glutamate (DeFelipe *et al.*, 1988; Kharazia and Weinberg, 1993), of pyramidal cells in different cortical areas may also influence various aspects of the integration of inputs along the dendrites. For example, the peak spine density along dendrites of pyramidal cells in TE, which contains neurons able to distinguish complex visual features (for a review, see Gross *et al.*, 1993), is more than three times higher than that found in V1 (Elston *et al.*, 1999a), which contains neurons that respond to relatively simple visual stimuli. As well as the obvious difference in the total number of putative excitatory inputs along the dendrite, differences in their density may influence local summation of post-synaptic potentials, or cooperativity between inputs (Shepherd *et al.*, 1985), being more likely to occur in highly spinous than in less spinous dendrites. Regional differences in the morphology of spines (Elston *et al.*, 1999a,b; Benavides-Piccione *et al.*, 2003) may also influence their functional properties (for reviews, see Shepherd, 1998; Koch, 1999). In conjunction, the regional differences in the size, branching pattern and spine density of pyramidal cells results in impressive variation in the total number of putative excitatory inputs sampled by each pyramidal cell in different cortical areas. For example, Layer III pyramidal cells in macaque area TE contain, on average, >11 times more spines in their basal dendritic arbours than those in macaque V1. Layer III pyramidal cells in macaque STP contain, on average, >13 times more spines in their basal dendritic arbours than those in macaque V1 (Elston *et al.*, 1999a).

Recent studies have revealed variation in the density, distribution and connectivity of inhibitory interneurons in different cortical areas (Hof and Nimchinsky, 1992; Kritzer *et al.*, 1992; Kondo *et al.*, 1994; Hof *et al.*, 1995; Goodchild and Martin, 1998; DeFelipe *et al.*, 1999; Dombrowski *et al.*, 2001; Elston and González-Albo, 2003), which are known to influence the receptive field properties of neurons (for reviews, see Kaas, 1991; Gilbert *et al.*, 1996; Jones, 2000; Angelucci *et al.*, 2002; Calford, 2002). As different classes of inhibitory neurons project to different regions of the pyramidal cell, including the dendrites, soma and axon, they may modulate different aspects of pyramidal cell activity (for reviews, see DeFelipe and Fariñas, 1992; Somogyi *et al.*, 1998). For example, axon termi-



A	auditory	FST	fundus of the superior temporal	PA	periamygdaloid	RL	rostrolateral auditory
A1	primary auditory	FV	frontoventral	Pall	periallocortex	SI	primary somatosensory area
AL	anterolateral auditory belt	Ig	insular granular	PIP	posterior intraparietal	SII	second somatosensory
AIT	anterior inferotemporal	Id	insular dysgranular	PIR	piriform	SMA	supplementary motor
Aud PB	auditory parabelt	IT	inferotemporal	PIT	posterior inferotemporal	TE	cytoarchitectonic area
c	caudal	L	lateral auditory	PL	prelimbic	TEO	cytoarchitectonic area
CA1	hippocampus	LIP	lateral intraparietal	PMD	premotor dorsal	TF	cytoarchitectonic area
CA3	hippocampus	m	medial	PMV	premotor ventral	TH	cytoarchitectonic area
CIT	central inferotemporal	M	medial visual	PO	parieto-occipital	v	ventral
CM	caudomedial	M1	primary motor	PP	posterior parietal	VIP	ventral intraparietal
d	dorsal	MDP	mediodorsal parietal	PrCO	precentral opercular	VP	ventroposterior
DI	dorsointermediate	MEF	medial eye field	PRO	proisocortex	VPP	ventroposterior parietal
DL	dorsolateral	MIP	medial intraparietal	PS	posterior sylvian	VS	ventral somatosensory
DM	dorsomedial	MST	middle superior temporal	PV	parietoventral	V1	primary visual
DP	dorsoparietal	MT	middle temporal	r	rostral	V2	second visual
ER	entorhinal	MTc	middle temporal crescent	R	rostral auditory	V3	third visual
FEF	frontal eye field	p	posterior	Ri	retroinsular	V4	fourth visual

Figure 3. Schematics illustrating cortical organization in the (*A*) owl monkey, (*B*) marmoset monkey and (*C*) macaque monkey. Although cytoarchitecture, myeloarchitecture, patterns of connectivity and neuronal response properties provide a basis for distinguishing cortical areas, their number, location and nomenclature remain controversial (for reviews, see Kaas, 1997; Rosa, 1997; Zeki, 2003). Graphs (*D–F*) illustrate differences in the total number of spines in the basal dendritic arbour of the 'average' layer III pyramidal cell in the primary visual area (V1, purple), the second visual area (V2, green), the fourth visual area (V4 or DL, blue), cytoarchitectonic area TEO (PIT or ITc, yellow) and cytoarchitectonic area TE (CIT or ITr, red). The numbers of spines within the dendritic arbours were determined by combining data from the Sholl analysis and spine density counts (see Elston, 2001). Figure modified from Elston (2003b).

nals of parvalbumin-immunoreactive chandelier cells form synapses with the axon initial segment of pyramidal cells and are thought to generate a powerful inhibitory influence over pyramidal cell discharge (Stuart and Häusser, 1994), whereas calbindin- and calretinin-immunoreactive double bouquet and bipolar interneurons project primarily to the dendrites of pyramidal cells and are believed to provide a means of modulating activity within their dendritic arbours. Thus, differences in the density, distribution and connectivity of the various classes of interneurons in different cortical areas is likely to contribute to regional differences in inhibitory function (e.g. Wang *et al.*, 2000, 2001; Constantinidis *et al.*, 2002). In addi-

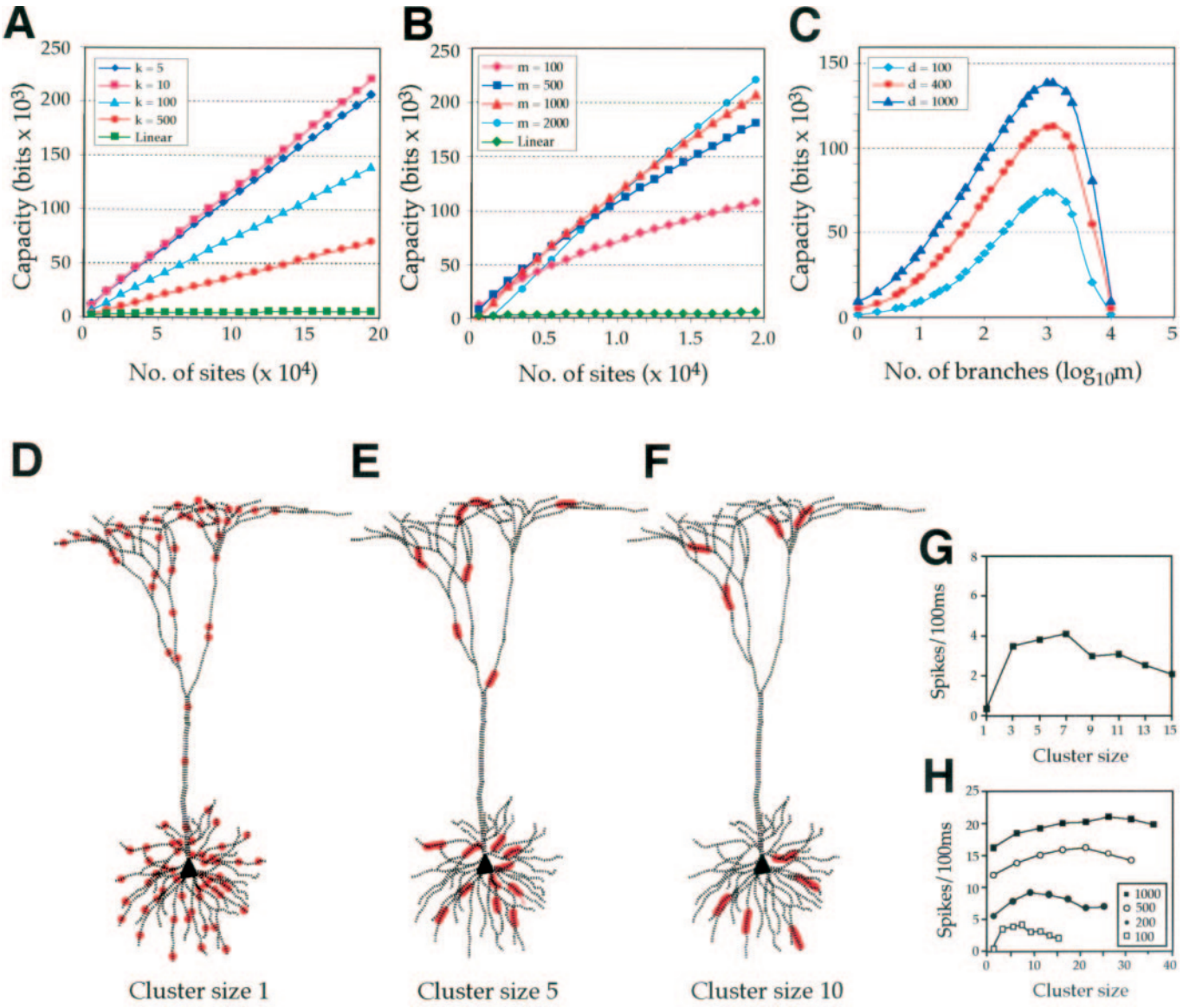


Figure 4. The capacity (measured in bits) of a cell of fixed branch length, or branch count, increases with an increase in the number of sites. Cells of different branch length (k) and branch count (m) are illustrated in (*A*) and (*B*), respectively. An increase in either of these variables results in increasing capacity with an increase in the number of sites. The capacity of a cell of fixed size (*C*) increases to a peak with an increase in the number of branches, before decreasing to values expected by linear models. (*D–F*) Drawings of the same pyramidal cell with a fixed number of synchronously active excitatory inputs (red circles) distributed throughout the dendritic arbour in different cluster sizes. (*G*) Plot of baseline cell activity versus cluster size, illustrating the different saturation levels for cells receiving different numbers of synchronously active excitatory inputs. (*H*) Increasing the number of inputs (with a set cluster size) also increases the number of spike discharges. Adapted from Mel (1993) and Poirazi and Mel (2001).

tion, as many inhibitory inputs in cortex synapse with spiny dendrites (Beaulieu and Colonnier, 1985; Beaulieu and Somogyi, 1990; Blümcke *et al.*, 1991; DeFelipe and Jones, 1991; Beaulieu *et al.*, 1992; del Rio and DeFelipe, 1994, 1997; Micheva and Beaulieu, 1995), it is probable that there are differences in the number of inhibitory inputs to pyramidal cells in the different cortical areas: the large branched arbours of cells in STP are likely to receive more inhibitory inputs than smaller, less branched cells in V1 or V2, for example. The distribution of these in markedly different dendritic arbours may also influence vetoing, or shunting inhibition (for reviews, see Emerson *et al.*, 1985; Koch and Poggio, 1985; Elston and DeFelipe, 2002).

Systems Level

Cortical circuits comprise many tens of thousands of neurons. Thus, any functional difference endowed at the neuronal level by specialization in pyramidal cell structure must necessarily then be amplified in the cortical circuitry. It follows that the extent of the cellular specialization, and differences in the numbers of cells within a network, may determine the functional capabilities of the cortical circuits. Surprisingly few studies have addressed this issue, and those that have have revealed spectacular results. Fuster and colleagues revealed that the discharge properties of neurons in V1 differed from those in inferotemporal (IT) cortex, those in the former being characterized by phasic discharge properties whereas those in the latter

are characterized by tonic activity (Ashford and Fuster, 1985; see also Fuster and Alexander, 1971; Fuster and Jervey, 1981, 1983; Miller *et al.*, 1993; Miyashita *et al.*, 1993a,b; Melchitzky *et al.*, 2001a,b). Similar findings have been reported for highly spinous cells in parietal cortex (cf. Gnadt and Andersen, 1988; Koch and Fuster, 1989; Colby *et al.*, 1996; Constantinidis and Steinmetz, 1996; Zhou and Fuster, 1996, 1997; Elston and Rosa, 1997; Chafee and Goldman-Rakic, 1998; Elston and Rockland, 2002). This persistent neural activity is now widely accepted to be important for 'holding' a memory (for reviews, see Fuster, 2000; Miller and Cohen, 2001). Further evidence for regional variation in the functional characteristics of cortical circuitry comes from the work of Murayama *et al.* (1997), who demonstrated that tetanic stimulation of somata led to long-term potentiation in TE, but long-term depression in V1.

Visual processing, however, occurs in multiple cortical areas, not just the primary visual area or TE. Imaging studies reveal that the number of areas recruited at any given time depends on the visual task. Neural ensembles may be activated across various cortical areas. This leads us to an important point: not all aspects of visual processing are performed by all visual neurons, nor are neurons in all visual areas recruited for any given visual task. Neurons in different areas reportedly process different aspects of vision, being loosely grouped into those that process for motion detection and those that process for object recognition (Ungerleider and Mishkin, 1982; Livingstone and Hubel, 1984; Felleman and Van Essen, 1991; but see Lennie, 1998). These basic differences in visual function are likely to be determined by gross differences in patterns of connectivity and the projections they receive (for reviews on connectivity, see Casagrande and Kaas, 1994; Lund *et al.*, 1994; Shipp and Zeki, 1995; Rockland, 1997, 2003; Bullier *et al.*, 2001). However, cortical connections are complex (Young, 1992, 1993) and objective analysis of corticocortical connections at the gross level fails to account for areal differences in specific aspects of neural function, such as discharge properties, direction selectivity and orientation selectivity.

Various theories exist for multiarea processing, including hierarchical and distributed models (for reviews, see Felleman and Van Essen, 1991; Mountcastle, 1995). Common to both models is that ensembles of neurons in multiple cortical areas may be co-activated for any given task. How regional differences in pyramidal cell structure may influence processing within these different models has been covered in detail elsewhere (Elston, 2003b). Briefly, within hierarchical models the flow of visual inputs through a pathway allows individual neurons within progressively 'higher' areas to process inputs from a proportionately larger region of the visuotopic map. The potential advantage of such 'serial reconstruction' of the visual scene is conceptually straight forward in the occipitotemporal pathway, where neurons in successively higher visual areas distinguish more complex features (for reviews, see Elston, 2003b; Fujita, 2003; Lund, 2003). Within a distributed system, co-activation of ensembles of highly spinous pyramidal cells in association areas may be important for binding sensory perceptions (for reviews, see Singer and Gray, 1995; Llinás and Paré, 1996). In addition, there is a greater potential for recurrent excitation through re-entrant circuits composed of neurons that integrate large numbers of excitatory inputs and are highly interconnected than in circuits composed of sparsely interconnected neurons that sample relatively few inputs (for a review, see Wang, 2001). Thus, co-operativity of ensembles of pyramidal cells of varying phenotype in different cortical areas potentially leads to a richness of diversity of, and functional cohesiveness in, cortical function not attainable in cortex composed of the same basic repeated circuit.

In summary, systematic areal specializations in cortical circuitry are likely to influence various aspects of visual processing. The small pyramidal cells in V1, and the circuits they form, allow high fidelity sampling of the visual scene, the relatively small number of inputs they integrate, and their patterns of connectivity, being instrumental in determining their phasic discharge properties (e.g. Ashford and Fuster, 1985). V1 circuit structure is specialized to subserve rapid processing of a constantly changing visual scene, allowing quick reset time for processing saccadic inputs. In other words, V1 circuitry is specialized to fire and flush. The integrative ability and patterns of connectivity of the larger, more branched and more spinous pyramidal cells in visual areas in IT cortex provide an anatomical substrate for the global integration of the visual scene. Each neuron's ability to sample a large number of excitatory inputs is central to the tonic activity reported in these cells, which is widely believed to be important for visual memory.

Prefrontal Circuitry

Specialization in Prefrontal Circuitry

Recent observations of pyramidal cells in prefrontal cortex (PFC) of man and macaques reveal that they are, in general, more branched and more spinous than their counterparts in the occipital, parietal and temporal lobes (Lund *et al.*, 1993; Elston, 2000; Elston *et al.*, 2001; Jacobs *et al.*, 2001). Layer III pyramidal cells in macaque monkey PFC have a peak branching complexity which, on average, is twice that of cells in V1 (Elston, 2000). Those in human PFC have a peak branching complexity more than three times that of cells in V1 (Elston *et al.*, 2001). Spine densities along their basal dendrites also vary markedly, with the average peak spine density of cells in PFC (>30 spines per 10 μm) being more than four times greater than that in V1. The peak spine density in human prefrontal cells is as high as 61 spines per 10 μm. Consequently, layer III pyramidal cells in macaque monkey PFC are, on average, up to 16 times more spinous than those in macaque V1 (Elston *et al.*, 2001) (Fig. 5) Layer III pyramidal cells in human PFC are, on average, 23 times more spinous than those in macaque V1. These differences cannot be attributed to scaling in cell structure, but reflect regional and species specializations (e.g. Elston and Jelinek, 2001; Jelinek and Elston, 2001).

How might PFC Circuitry Subserve Cognitive Processing?

Neurons in the prefrontal cortex of man and macaque are characterized by sustained tonic activity, particularly those in the dorsolateral PFC (e.g. Fuster and Alexander, 1971; Kubota and Niki, 1971; Fuster, 1973; Funahashi *et al.*, 1989; Leung *et al.*, 2002). In the above section it was argued that cortical circuits, such as those in IT cortex, which are composed of highly branched, spinous pyramidal cells, provide an anatomical substrate for sustained neural discharge, whereas those composed of less-branched pyramidal cells with relatively few spines, such as in V1, provide a platform for phasic neural discharge. Pyramidal cells in PFC of man and macaque have a more complex structure than those in IT. Given the preceding

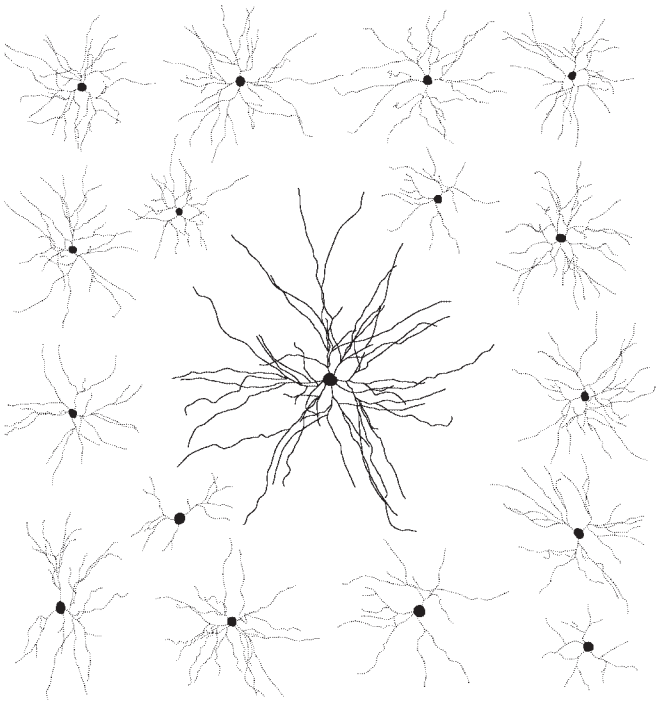


Figure 5. Scale drawings of the basal dendritic arbours (in the tangential plane) of layer III pyramidal cells of the prefrontal cortex (black) and the primary visual area (V1, grey) of the macaque monkey. Prefrontal cells are, on average, up to 16 times more spinous than those in V1 (see Elston, 2000). As each dendritic spine receives at least one excitatory input, cells in area 12 potentially integrate 16 times more excitatory inputs than those in V1.

logic, it would therefore be expected that their even more complex structure would endow PFC circuitry with more complex functional capabilities. This is reportedly so; cells in PFC differ from those in other cortical areas in that they remain active during the delay between cue and related execution despite interference from distractors (Miller *et al.*, 1996). Persistent activity reported for neurons in other areas is disrupted by distractors (Miller *et al.*, 1993, 1996; Constantinidis and Steinmetz, 1996). Based on this difference, Miller and Cohen (2001) conclude that, 'posterior cortical neurons reflect the most recent input regardless of its relevance, whereas the PFC selectively maintains task-relevant information'. Moreover, neural reactivity to sensory stimuli is reportedly less sensitive in PFC than in sensory association cortex (Kojima, 1980; Kubota *et al.*, 1980; Fuster and Jervey, 1982; Miller *et al.*, 1996). An overview of patterns of projections to, and within, prefrontal cortex reveals why specialization of the PFC pyramidal cell phenotype may influence its ability to 'hold' task-relevant information even in the presence of distractors.

PFC receives a diverse set of corticocortical inputs from a multitude of areas involved in processing all sensory modalities (for reviews, see Fuster, 1985, 1997; Cavada *et al.*, 2000; Pandya and Yeterian, 2000; Petrides, 2000; Rolls, 2000). In addition, cortical areas within prefrontal cortex multiply interconnected (e.g. Barbas and Pandya, 1989; Pandya and Barnes, 1987; Preuss and Goldman-Rakic, 1991b). Thus, pyramidal cells in PFC potentially process large numbers of diverse inputs. While it could be argued that the persistent neural activity in PFC results solely from a continual bombardment of such inputs, this explanation cannot account for the type of persistent activity reported for neurons in prefrontal cortex, nor for those prefrontal functions that do not require direct sensory input. Moreover, there are many other cortical regions that receive a multitude of inputs from diverse sources (e.g. Andersen *et al.*, 1990; Cavada *et al.*, 1997; Lewis and van Essen, 2000). Thus, it appears likely that some aspect of prefrontal circuitry may subserve the sustained neural activity characteristic of PFC.

The superficial layers in PFC, like those in sensory cortex (Juliano *et al.*, 1990; Huntley and Jones, 1991; Lund *et al.*, 1993), are characterized by horizontal intrinsic axon projections that arise from supragranular pyramidal cells (Kritzer and Goldman-Rakic, 1995; Pucak *et al.*, 1996; González-Burgos *et al.*, 2000; Melchitzky *et al.*, 2001a,b). However, the topography of these projections in PFC differs somewhat from those reported in sensory cortex: intrinsic horizontal projections in sensory areas tend to be restricted to a relatively small region of cortex surrounding their origin, whereas those in PFC are more widespread. In the primary visual cortex, these axon projections terminate in relatively dense 'clusters' (Rockland and Lund, 1982, 1983; Rockland *et al.*, 1982; Livingstone and Hubel, 1984; Martin and Whitteridge, 1984; Rockland, 1985; Kisvárday *et al.*, 1986; McGuire *et al.*, 1991). The size and spread of intrinsic clusters is more widespread and diffuse in extrastriate visual areas (Yoshioka *et al.*, 1992; Lund *et al.*, 1993; Levitt *et al.*, 1994; Fujita and Fujita, 1996), but the relative differences in the dimensions of the clusters in visual areas corresponds to the diameter of the basal dendritic arbours of supragranular pyramidal cells (Lund *et al.*, 1993; Elston *et al.*, 1999a). In PFC, however, these intrinsic axonal projections form less regular arbours, which extend up to 8 mm (Levitt *et al.*, 1993; Kritzer and Goldman-Rakic, 1995; Pucak *et al.*, 1996). The average diameter of the pyramidal cell arbours is considerably greater than the width of the intrinsic stripes in PFC (~400 and 267 μm, respectively), but slightly less than the centre-to-centre spacing (536 μm) (Levitt *et al.*, 1993; Elston, 2000). These differences in the size of the basal dendritic arbours and intrinsic axonal arbours may allow different sampling strategies in cortex (Fig. 6). Potentially, individual neurons in PFC sample a larger number of more diverse monosynaptic excitatory inputs over a more expansive region of cortex than in sensory cortex.

The Pyramidal Cell in the Evolution of PFC and Executive Cortical Function

We have already seen that in humans and macaque monkeys, pyramidal cells in prefrontal cortex are structurally complex and that PFC circuitry may be endowed with specialized functional capabilities. The correlation between human PFC pyramidal cell complexity and human cognitive abilities may suit well our view that we are a highly cognate species. The macaque data also sit well with this interpretation. However, this is clearly not a satisfactory way to determine any possible correlation between the evolution of PFC cell structure and cognitive abilities (for reviews, see Preuss, 1995, 2000). Instead, a broad survey of pyramidal cell structure should be undertaken in a number of primate and non-primate species to correlate structural modification of PFC with cognitive styles. With these objectives in mind, we have begun to study pyramidal cell structure in other primate species.

Our first objective has been to study pyramidal cell structure in New World monkeys, which separated from the Old World lineage during the late Eocene period (Fleagle, 1999). We found

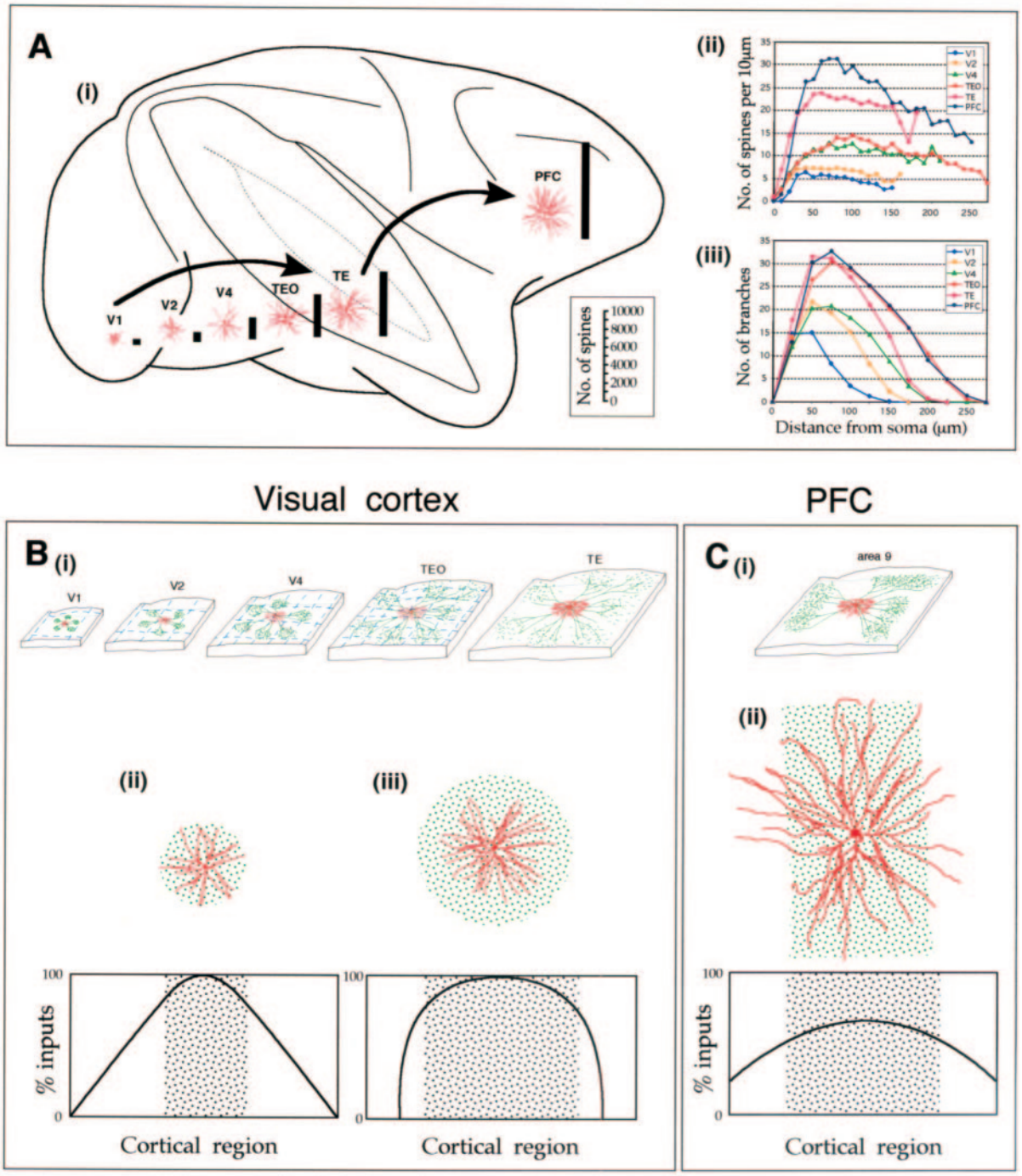


Figure 6. (*A*) Schematic of (i) the macaque brain illustrating one of many pathways to prefrontal cortex (e.g. Wilson *et al*., 1993; Rao *et al*., 1997; Ó Scalaidhe *et al*., 1997). Neurons in the primary visual area (V1), second visual area (V2), fourth visual area (V4), cytoarchitectonic areas TEO and TE and prefrontal cortex (PFC, Walker's area 12) are illustrated to show differences in the size and branching patterns of their basal dendritic arbours. The number of individual dendritic spines, the site of excitatory inputs, found in the basal dendritic arbour of the 'average' layer III pyramidal cell in each area is illustrated (solid bars). Note there is a progressive increase in the putative number of excitatory inputs that project to individual pyramidal cells with anterior progression through these areas. Plots of (ii) the spine density and (iii) branching patterns illustrate marked variation between populations of neurons in the different cortical areas (for a review, see Elston and DeFelipe, 2002). (*B*) Schematics of cortical slices in V1, V2, V4 and TEO (i) illustrating how the progressive increase in size of the basal dendritic arbours (red cells) coupled with visuotopic compression (dashed blue lines) result in a >100-fold difference in the receptive field properties of neurons between V1 and TEO (ii). The progressive increase in the horizontal extent of these intrinsic clusters (green dashed lines) through these areas results in an even greater proportion of the visuotopic representation being sampled by individual neurons, which may account for the 1000-fold difference in receptive field size determined by electrophysiological recording in V1 and TEO. We suggest that the size of the dendritic arbours and intrinsic axonal projections in inferotemporal cortex are essential for global aspects of visual processing such as object recognition. Despite differences in the size of both the axon clusters and the size of the basal dendritic arbours in these areas, both have approximately the same dimension in each area (ii), resulting in specialized sampling geometry (for a review, see Malach, 1994). In area TE, however, the intrinsic projections are more widespread and more diffuse (iii), resulting in a different sampling geometry (note that receptive fields of neurons in TE are so large that this area is not topographically organized; the receptive field of many neurons includes almost the entire field of view). (*C*) Schematics of a cortical slice taken from PFC (i) illustrating the widespread stripe-like intrinsic projections in PFC (as reported in area 9). In PFC, the basal dendritic arbours are larger than the width of the intrinsic stripes (ii), potentially resulting in more complex connectivity within cortex through greater convergence to individual neurons. Moreover, pyramidal cells in PFC may be characterized by different sampling strategies according to the axis of the intrinsic axon stripes.

that pyramidal cells in prefrontal cortex of New World marmoset monkeys have a relatively simple structure, being less than six times more spinous than those in V1 (cf. Elston *et al.*, 1999b, 2001). [Note that in both New World and Old World primates studied to date, estimates of the number of spines found in the basal dendritic arbours of layer III pyramidal cells in V1 are remarkably similar (597–773).] The relative simplicity of their structure, however, does not reflect a basic characteristic of pyramidal cells in their brain. Pyramidal cells in marmoset visual cortex, for example, are characterized by the same progressive increase in structural complexity with anterior progression through occipitotemporal (OT) areas as seen in humans and macaque monkeys (Fig. 7). Indeed, cells in marmoset anterior IT (ITr, the homologue of macaque TE) are seven times more spinous than those in V1 (Fig. 7). The study of pyramidal cell structure in another New World monkey, *Aotus*, reveals a similar trend: pyramidal cells in PFC are ~2.6 times more spinous than those in V1, whereas those in ITr are ~4.8 times more spinous than cells in the primary visual area (Fig. 7). [Although these data were sampled from an aged animal and may have been influenced by age-related spine loss, the relative trends in OT and prefrontal cortex are noteworthy.] In absolute terms, our estimates reveal that human prefrontal pyramidal cells have, on average, 15 138 spines in their basal arbours (Brodmann's area 10), 72% more than those in macaque (8766, Preuss and Goldman-Rakic's area 10), 3.8 times more than those in marmoset (3983, Brodmann's area 10) and 7.5 times more than those in *Aotus* (2031, dorsolateral granular PFC).

Given the differences in the structural complexity of the pyramidal cell in the granular PFC, we might expect that the degree of interconnectivity between neurons (both intrinsic and extrinsic) varies between different primate species. For example, according to the mathematical laws of convolution, if there is an increase in the number of inputs sampled by pyramidal cells, there must be an increase in the number of inputs to them. Unfortunately, there are few comparative studies on patterns of connectivity in the PFC of different primates. None the less, studies in the New World squirrel monkey and the galago reveal that the extent and density of prefrontal connections is less than that in macaque monkeys (Bugbee and Goldman-Rakic, 1983; Preuss and Goldman-Rakic, 1991b). These differences in the patterns of axon projections and the number of putative excitatory inputs sampled by individual pyramidal cells are then likely to result in different cellular/circuit function in PFC of different primate species (see Goldman-Rakic, 1995). These differences, in turn, would influence the cognitive abilities between species. The striking simplicity of this hypothesis makes it particularly appealing, especially when considered in the context of the vast body of evidence on the relationship between pyramidal cell structure and function/behaviour in development, maturation, senescence and disease. Based on this hypothesis we would predict that neural activity in marmoset or owl monkey PFC would differ from that reported in macaques, and that in macaques would differ from that in humans. It should be possible to test this hypothesis directly by electrophysiological recording in non-human species.

What then may act as a selective pressure for the evolution of more spinous pyramidal cells during cortical expansion? As pointed out by Ringo (1991), cortical expansion through the addition of more of the same basic cortical unit (or module) results in an overall decrease in connectivity in the brain. Processing in a larger brain would necessarily involve a larger number of synaptic connections (over a longer distance) for information to flow between distant modules than in a smaller brain. The addition of a sufficient number of modules (canonical circuits) to account for the 1000-fold difference in the size of mammalian brains would inevitably result in the segregation of processing into different foci. Theoretically, processing would become divergent and would be relatively slow. This problem may be avoided by adding more complex 'modules', i.e. by adding progressively more complex, highly interconnected, pyramidal cells. Said in another way, the addition of new prefrontal circuitry composed of V1-type pyramidal cells in the human brain would not result in the same functional advantage for human mentation as the addition of new circuitry composed of human PFC-type pyramidal cells.

Conclusions

The present data reveal three interesting features related to specialization in pyramidal cell structure and cortical expansion during primate evolution. First, the trend for increasing pyramidal cell complexity with anterior progression in occipitotemporal cortex was likely to be present in a common ancestor of anthropoids (Elston *et al.*, 1999b; Elston, 2003a). Secondly, it is unlikely that a common ancestor of anthropoids had highly branched, spinous pyramidal cells in their PFC. Thirdly, the PFC pyramidal cell phenotype has become highly complex in only some anthropoids. The recent expansion of PFC in humans

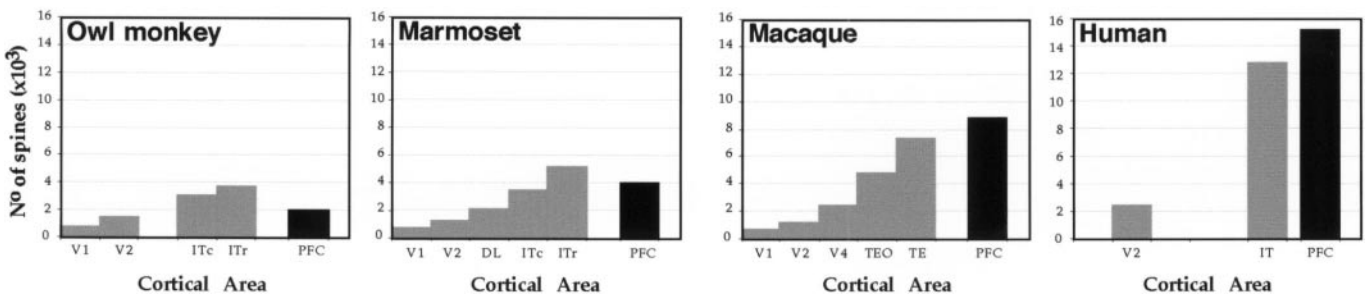


Figure 7. Plots of the estimates of the total number of spines in the basal dendritic arbour of the 'average' pyramidal cell in occipitotemporal (grey) and prefrontal cortex (black) in the owl monkey, marmoset monkey, macaque monkey and human. The spine count increases with anterior progression through occipitotemporal cortex in all species. The prefrontal pyramidal cell phenotype, however, differs markedly between species. In the New World marmoset and owl monkeys, the prefrontal pyramidal cell has relatively few spines, whereas in Old World macaque monkeys and humans it is extremely spinous. Data taken from Elston et al. (1999a,b, 2001) and Elston (2003d).

(Stephan *et al.*, 1981) is paralleled by a dramatic increase in pyramidal cell complexity. The smaller PFC of the macaque is composed of less complex pyramidal cells and that of marmosets and owl monkeys of even less complex cells. Accepting that the complexity of cortical circuitry (i.e. its individual components) determines its functional capabilities, differences in the degree of complexity of PFC pyramidal cells necessarily influence PFC function. As cognition is often associated with PFC, differences in the structure of PFC in different species are likely to influence their cognitive styles. In the future, it will be of interest to study pyramidal cell structure in great apes, which, like man, have greatly enlarged frontal lobes (Semendeferi *et al.*, 2002). In addition, further experiments are required to determine the physiological characteristics of prefrontal circuitry in the different species and to determine if the results parallel the structural complexity of PFC pyramidal cells. The importance of regional specialization in neocortical pyramidal cell structure in determining cognitive styles is summarized below.

- Pyramidal cell structure varies in different areas of the cortex.
- As the pyramidal cell is the most ubiquitous neuron in cortex, regional variations in its structure are likely to underlie fundamental differences in cortical circuitry.
- Cortex composed of different circuitry is likely to have different functional capabilities.
- The systematic nature of specialization in pyramidal cell structure in functionally related cortical areas suggests it may be important in cooperative function between cortical areas.
- The extent to which cortical circuitry has become specialized, and the extent to which circuitry may influence cortical function, is species dependent.
- Variation in the degree of complexity of pyramidal cell structure in the PFC of different anthropoid species is likely to influence their cognitive styles.
- Further comparative studies are required if we are to gain a better understanding of the role of pyramidal cell specialization during PFC expansion and the evolution of executive brain function.
- It is unlikely that any correlation between pyramidal cell structure and cognitive ability is absolute. In particular, it does not necessarily follow that the most complex pyramidal cell structure endows a species with superior intelligence.

Notes

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Address correspondence to Guy N. Elston, Vision, Touch and Hearing Research Centre, Department of Physiology and Pharmacology, School of Biomedical Sciences, The University of Queensland, Queensland 4072, Australia. Email: g.elston@vthrc.uq.edu.au.

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