The Pyramidal Cell in Cognition: A Comparative Study in Human and Monkey

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Here we present evidence that the pyramidal cell phenotype varies markedly in the cortex of different anthropoid species. Regional and species differences in the size of, number of bifurcations in, and spine density of the basal dendritic arbors cannot be explained by brain size. Instead, pyramidal cell morphology appears to accord with the specialized cortical function these cells perform. Cells in the prefrontal cortex of humans are more branched and more spinous than those in the temporal and occipital lobes. Moreover, cells in the prefrontal cortex of humans are more branched and more spinous than those in the prefrontal cortex of macaque and marmoset monkeys. These results suggest that highly spinous, compartmentalized, pyramidal cells (and the circuits they form) are required to perform complex cortical functions such as comprehension, perception, and planning.

Key words: cortex; dendrite; spine; primate; macaque; marmoset; prefrontal; temporal; occipital

Despite Ramon y Cajal's original observations of variation in the morphology of pyramidal cells in different species (Ramon y Cajal, 1894), the isocortex was and still is considered by many to be uniform in structure and composed of a repeated basic circuit (Szentagothai, 1975; Creutzfeldt, 1977; Rockel et al., 1980; Eccles, 1984; Douglas et al., 1989; Mountcastle, 1995). The application of new methods of analyses (Elston, 2001) has revealed a remarkable degree of variation in pyramidal cell morphology between different visual areas (Elston and Rosa, 1997, 1998, 2000; Elston et al., 1999a,b; see also Lund et al., 1993). In addition, cells in the macaque prefrontal cortex (PFC) are considerably more branched and more spinous than those in the occipital, parietal, and temporal lobes (Elston, 2000). The highly modified phenotype found in the PFC has been interpreted as being essential in determining the integration of diverse inputs (Elston, 2000) reportedly necessary for executive cortical function (Goldman-Rakic, 1999). However, it remains to be determined whether human's ability to perform complex cognitive functions is solely attributable to the increase in the number of cortical cells and areas or whether the human PFC pyramidal cell differs from that of other species. To evaluate the possibility that the pyramidal cell in the PFC of humans may differ from that in other primates, we injected cells in corresponding cortical regions of the New World marmoset monkey (*Callithrix jacchus*), the Old World macaque monkey (*Macaca fascicularis*), and human. We found marked differences in the pyramidal cell phenotype between sensory, sensory-association, and executive cortex in humans. Moreover, we found clear differences in the pyramidal cell phenotype in corresponding brain regions between monkeys and humans.

MATERIALS AND METHODS

Cell morphology was studied in primate species characterized by brains of markedly different size and degree of gyrencephalization (Fig. 1*a–c*). The cortical areas studied included the second visual area (V2), the ventromedial region of the inferior temporal cortex (Brodmann's area 21 of humans, TEa of macaques, and ITr of marmosets), and the anterior frontal lobe (Brodmann's area 10). Cortical areas were identified based on previously published electrophysiological, connectional, myeloarchitectonic, and cytoarchitectonic studies (Brodmann, 1907, 1909; Walker, 1940; Seltzer and Pandya, 1978; Preuss and Goldman-Rakic, 1991; Sereno et al., 1995; Rosa et al., 1997; Elston et al., 1999b). Human tissue was obtained 2 hr postmortem from the left hemisphere of a 48-year-old normal male and immersed in 4% paraformaldehyde for 24 hr. Macaque prefrontal cortex was derived from the left hemisphere of a 10-year-old male, whereas occipital and temporal cortex were taken from the left hemispheres of 18-month-old males (AM1 and DM4, respectively) (Elston and Rosa, 1998; Elston et al., 1999a). Marmoset PFC was taken from an 18-month-old male (M908), the temporal lobe was taken from the left hemisphere of 24- to 28-month-old males (BS10 and ML7), and the occipital cortex was taken from the left hemispheres of 24- to 27-month-old males (BS10 and CJ715) (Elston et al., 1999b). Monkeys were overdosed by lethal injection of sodium pentobarbitone and were perfused intracardially with 4% paraformaldehyde.

Sections (250 μm) cut tangential to the cortical surface with the aid of a vibratome were prelabeled with 4,6-diamidino-2-phenylindole (D9542;

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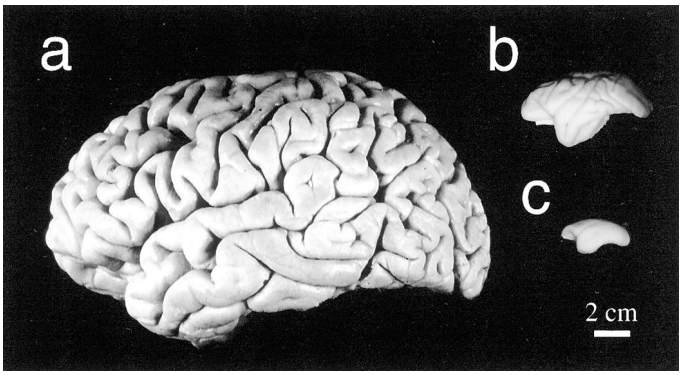

Figure 1. Scale images of the human (*a*), macaque (*b*), and marmoset (*c*) brains showing the relative differences in size and gyrencephalization between species. Note the difference in the size of the cortical lobes. The frontal lobe in humans comprises a greater proportion of the entire cortex than in macaque or marmoset monkeys.

Sigma, St. Louis, MO). By relating the tangential sections to traditional transverse sections we were able to identify the border between layers III and IV. In addition, by focusing through the thickness of the tangential slice, the cytoarchitectural differences between these layers were readily distinguished, enabling the identification and injection of cells at the base of layer III [Elston and Rosa (1997), their Fig. 3]. Furthermore, in each case neurons were also injected in other sections in each series, allowing the identification of all layers (our unpublished results). Cell injection methodology has been described in detail previously (Buhl and Schlote, 1987; Einstein, 1988; Elston and Rosa, 1997). Briefly, cells were injected with Lucifer yellow (8% in 0.1 M Tris buffer, pH 7.4) by continuous current. After injection of neurons, the sections were first processed with an antibody to Lucifer yellow [1:400,000 in stock solution: 2% bovine serum albumin (A3425; Sigma), 1% Triton X-100 (30632; BDH Chemicals, Poole, UK), and 5% sucrose in 0.1 M phosphate buffer] and then with a biotinylated species-specific secondary antibody (1:200 in stock solution; RPN1004; Amersham Pharmacia Biotech, Little Chalfont, UK), followed by a biotin–horseradish peroxidase complex (1:200 in phosphate buffer; RPN1051; Amersham). 3,3′-diaminobenzidine (D8001; Sigma) was used as the chromogen.

The branching pattern of cells was determined by counting the number of dendritic branches that intersected with concentric circles (centered on the cell body) with increasing radii (25 μm increments) (Sholl, 1953). Dendritic field areas were determined by calculating the area contained within a polygon joining the outermost distal tips of the basal dendrites (Elston and Rosa, 1997). The density of spines on the dendrites of pyramidal cells was determined by counting the number of spines per 10 μm increment of 20 horizontally projecting dendrites of different cells in each cortical area (Valverde, 1967). The total number of spines found in the "average" pyramidal cell basal dendritic arbor was calculated by multiplying the average number of spines of a given portion of dendrite by the average number of branches for the corresponding region, over the entire dendritic arbor (Elston, 2001).

Table 1. Peak branching complexity, size, and spine density of the basal dendrites of layer III pyramidal cells

	Occipital	Temporal	Prefrontal
Peak branching complexity (mean ± SD)			
Marmoset	27.10 ± 4.51	33.23 ± 4.95	25.46 ± 5.54
Macaque	21.46 ± 5.47	31.54 ± 5.71	32.36 ± 4.41
Human	23.47 ± 3.54	30.90 ± 5.08	43.49 ± 8.40
Basal dendritic field areas ($\times 10^4$ μm^2) (mean ± SD)			
Marmoset	5.17 ± 0.73	10.71 ± 1.64	7.5 ± 1.4
Macaque	4.39 ± 1.07	8.19 ± 1.33	13.3 ± 1.99
Human	8.60 ± 0.94	15.35 ± 3.12	13.5 ± 1.89
Maximum spine density per 10 μm (mean ± SEM)			
Marmoset	6.8 ± 0.62	16.7 ± 0.80	20.6 ± 0.89
Macaque	7.3 ± 0.53	23.8 ± 1.56	24.0 ± 0.85
Human	11.75 ± 0.81	32.1 ± 1.6	32.5 ± 1.64

RESULTS

Three hundred and forty-four layer III pyramidal cells were included for analyses. Various aspects of cell morphology varied independently, including the branching patterns and spine densities of the dendrites. From Figure 2*a* it can be seen that the maximum number of dendritic branches for any distance from the cell body differed according to the cortical region and species (Table 1). Statistical analyses revealed that all within-species between-region comparisons were significantly different ($p < 0.05$), as were all within-region between-species comparisons. Integration of the areas under the curves revealed a consistent trend: cells in humans were more branched than those in macaques, which were more branched than those in marmosets, for any given cortical region. Cells in the frontal lobe of humans had approximately one-third more dendritic branches than those in macaques and twice as many as those in marmosets. Moreover, human prefrontal cells were the most branched of all cells studied. In addition, these data show a trend for more branched cells with progression from occipital to temporal and prefrontal cortex in both humans and macaques. Data for the marmoset, however, do not comply with this trend. Instead, cells in the prefrontal cortex of the marmoset were considerably less branched than those in its temporal lobe (ITr).

Comparison of branching patterns with the size of the dendritic arbors (Fig. 2*b,* Table 1) revealed no consistent correlation between the two variables. Moreover, comparison of the size of cells revealed that they are not necessarily correlated with brain

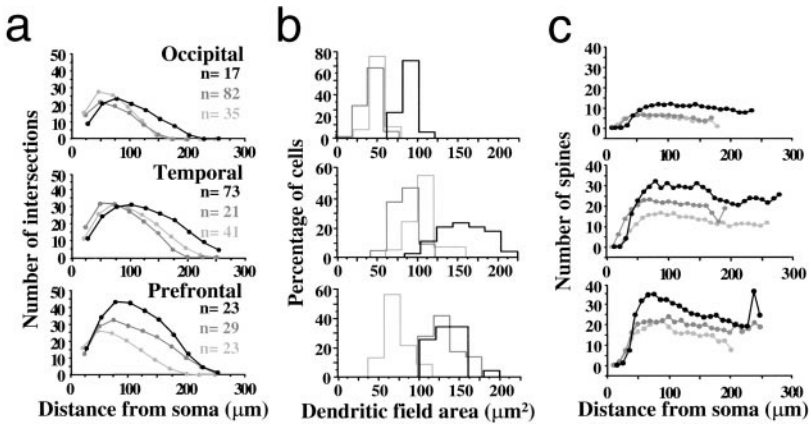

Figure 2. Plots of the number of dendritic branches (*a*), areas (*b*), and spine densities (*c*) of the basal dendritic arbors of layer III pyramidal cells sampled in the occipital (*top*), temporal (*middle*), and prefrontal (*bottom*) cortex of humans (*black*), macaques (*dark gray*), and marmosets (*light gray*).

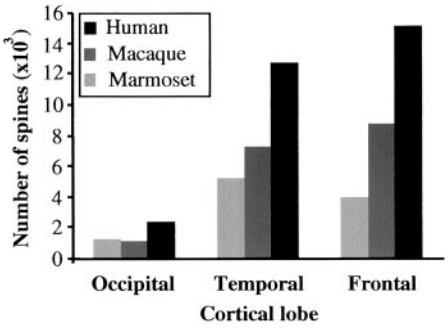

Figure 3. Plot of the estimates of the total number of spines in the basal dendritic arbor of the "average" pyramidal cell in the occipital, temporal, and prefrontal cortex of marmosets (*light gray*), macaques (*dark gray*), and humans (*black*). These calculations revealed that cells in the prefrontal cortex of humans and macaques (15,138 and 8766, respectively) are considerably more spinous than those in the temporal lobe (12,700 and 7260, respectively). In marmosets, however, cells in the prefrontal cortex (3983) were less spinous than those in the temporal lobe (5176).

size. An ANOVA ($F_{(343)} = 218$; $p < 0.0001$) and *post hoc* Fisher's PLSD tests ($p < 0.05$) revealed most comparisons of arbor size to be significantly different. However, there was no significant difference between the size of cells in the temporal lobe of macaques, the frontal lobe of marmosets, and the occipital lobe of humans. Nor was there any significant difference in the size of cells in the frontal lobe of humans and macaques.

To estimate how many excitatory inputs may be sampled by individual cells, we determined the number and distribution of spines within the dendritic arbors of cells in the occipital, temporal, and prefrontal cortex. Over 47,000 individual spines were reconstructed from 180 dendrites of different cells. In all three cortical regions studied, spine density was highest in humans, followed by macaques, and then marmosets (Fig. 2*c*, Table 1). A two-way repeated-measures ANOVA of the entire data set revealed spine densities to be significantly different between cortical regions and/or species ($F_{(3258)} = 188$; $p < 0.0001$). *Post hoc* two-way repeated-measures ANOVAs revealed that, with the exception of cells in the human temporal and prefrontal cortex, all within-species regional comparisons were significantly different ($p < 0.001$). Within-region between-species comparisons revealed significant differences ($p < 0.001$), except for cells in the occipital cortex of humans and macaques and cells in the temporal cortex of humans and macaques. By combining the data on branching patterns and spine density, we were able to estimate the number of spines in the basal dendritic arbor of the average cell in each area. These calculations revealed that cells in the PFC of humans and macaques (15,138 and 8766, respectively) were considerably more spinous than those in the temporal lobe (12,700 and 7260, respectively) (Fig. 3). In marmosets, however, cells in the frontal lobe (3983) were considerably less spinous than those in the temporal lobe (5176). In all three species, cells in the temporal lobe were more spinous than those in the occipital lobe (human, 2417; macaque, 1139; marmoset, 1240).

DISCUSSION

The present study shows that pyramidal cell morphology varies markedly between cortical regions in different anthropoid genera. These data extend previous findings of systematic differences in the pyramidal cell phenotype in the monkey cortex and reveal interareal differences in pyramidal cell morphology in the human cortex. In conjunction, the results provide substantial evidence for the thesis that pyramidal cells, and the circuits they form, are specialized for their functional requirements.

Methodological considerations

Data in the present study were, in the case of monkeys, sampled from different animals of varying developmental ages. As both dendritic processes and spines atrophy with aging (Scheibel et al., 1975; Lund et al., 1977; Huttenlocher, 1979; Bourgeois and Goldman-Rakic, 1993; Anderson and Rutledge, 1996; Jacobs et al., 1997), some interareal variation in the pyramidal cell phenotype reported here may be attributable to sampling error. However, in the macaque monkey, the most complex spinous cells were observed in the PFC of the oldest animal, which would have been subject to the greatest spine loss and dendritic regression. In the marmoset monkey, data from the PFC was sampled from a slightly younger animal than those from which occipital and temporal lobe data were sampled. Thus, it may be argued that prefrontal cells had not yet reached their peak, whereas those in the occipital and temporal cortex had done so (i.e., peak spine density in the PFC may occur at a later developmental age than in the occipital and temporal cortex). Although we are unaware of any published data on the age at which the peak spine density is reached in the marmoset occipital, temporal, and prefrontal cortex, peak spine density in both the occipital cortex and prefrontal cortex of humans and macaques is reached by ~1.5 years of age (Huttenlocher, 1979; Bourgeois et al., 1994; Anderson and Rutledge, 1996). As the marmoset prefrontal data were sampled from an animal that was 18 months of age, it is likely that peak spine density had already been reached.

Phenotypic variation and cell function

Various aspects of cell structure are reportedly critical in determining the subcellular, cellular, and systems function of neurons. Differences in the size and number of branches in the dendritic arbors of cortical pyramidal neurons affect the total number of spines contained within, reflecting putative differences in the number of excitatory inputs received by individual cells (Elston and Rosa, 1997, 1998; Elston et al., 1999a,b; Elston, 2000). Varying spine densities reported on the basal dendrites may also affect electrical and biochemical compartmentalization, cooperativity between inputs, and shunting inhibition (Koch et al., 1982; Shepherd et al., 1985; Rall and Segev, 1987; Shepherd and Brayton, 1987; Koch and Zador, 1993; Mainen, 1999). In addition, differences in the total length of, number of branches in, and diameters of the dendrites determine the cable properties (Rall, 1959), the degree of nonlinear compartmentalization (Rall, 1964; Koch et al., 1982), and the propagation of potentials (Stuart and Häusser, 1994; Spruston et al., 1995; Markram et al., 1997; Vetter et al., 2001) within the arbor (for review, see Rall et al., 1992; Stuart et al., 1997; Koch, 1999; Mel, 1999; Spruston et al., 1999; Häusser et al., 2000). Modeling studies have also shown that a greater potential for electrical compartmentalization in highly branched dendritic arbors may result in a significant increase in the capacity for learning and memory of a neuron by increasing the representational power of the cell (Poirazi and Mel, 2001). Thus, it appears likely that regional differences in pyramidal cell morphology contribute to area-specific aspects of cellular and systems function such as discharge properties and contrasting synaptic plasticity (Fuster and Alexander, 1971; Kubota and Niki, 1971; Fuster and Jervey, 1981; Ashford and Fuster, 1985; Miyashita and Chang, 1988; Funahashi et al., 1989; Murayama et al., 1997). As a logical extension, species differences in pyramidal cell morphol-

ogy (for corresponding brain regions) are likely to contribute to species-specific differences in cortical function. In particular, cells in the human PFC potentially compartmentalize a greater number of inputs within their dendritic arbors than those in the PFC of the macaque, and those in the PFC of macaque compartmentalize more than those in the PFC of the marmoset. Moreover, cells in the human PFC may integrate a greater diversity of inputs than those in other species.

On brain size and heterogeneity of the pyramidal cell phenotype

The present results clearly show that the size of and the number of branches and spines in the basal dendritic arbors of pyramidal cells may vary independently of each other. Some of these variables may be correlated with brain size, but others may not. For example, among the areas studied here, spine density appears to be correlated with brain size: spine density was consistently higher in humans compared with macaques and higher in macaques compared with marmosets for any of the given brain regions. However, the size of the cells does not necessarily correlate with brain size: cells in the occipital and temporal lobe of the marmoset were larger than those in corresponding cortical regions in the macaque. Moreover, pyramidal cells in different cortical regions and/or species are not merely scaled versions of the same type but are structurally different (Elston and Jelinek, 2001; Jelinek and Elston, 2001). In addition, the total number of spines in the basal dendritic arbor of the average cell in each cortical region did not correlate with brain size. Whereas cells in the PFC of humans and macaques were considerably more spinous than those in the temporal and occipital lobes, those in the PFC of marmosets were less spinous than those in the temporal cortex (Fig. 3). Marmoset PFC occupies a smaller fraction of its isocortex compared with the PFC of humans and macaques, and comprises fewer cortical areas (Gebhard et al., 1995). In contrast, the marmoset temporal lobe is relatively expansive and appears to be highly specialized for visual processing (Rosa, 1997). The second visual area is reportedly homologous across species (Sereno et al., 1995; Rosa et al., 1997), being a phylogenetically old cortical area (Kaas, 1992). Thus, the number of spines in the basal dendritic arbor of the average pyramidal cell in each area appears to reflect both the level of processing (sensory, sensory association, or executive function) and the extent to which a particular region has become specialized for the particular function.

Conclusions

The present results show that the enlargement of the cortex in higher primates has not occurred solely through the addition of new cortical areas of similar circuitry. Instead, the results suggest that pyramidal cell morphology in marmosets, macaques, and humans is specialized for their functional requirements in any given cortical region. In particular, prefrontal pyramidal cells have become more branched and spinous during the evolution of the PFC in higher primates, facilitating specialized cortical functions such as comprehension, perception, and planning. Differences in the branching structure of prefrontal pyramidal cells, and the number of spines they contain, are not correlated with brain size, but reflect fundamental differences in circuitry between species.

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