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Regional Dendritic Variation in Neonatal Human Cortex: A Quantitative Golgi Study

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Key Words
Development · Neocortex · Spine

Abstract
The present study quantitatively compared the basilar dendritic/spine systems of lamina V pyramidal neurons across four hierarchically arranged regions of neonatal human neocortex. Tissue blocks were removed from four Brodmann's areas (BAs) in the left hemisphere of four neurologically normal neonates (mean age = 41 ± 40 days): primary (BA4 and BA3-1-2), unimodal (BA18), and supramodal cortices (BA10). Tissue was stained with a modified rapid Golgi technique. Ten cells per region (N = 160) were quantified. Despite the small sample size, significant differences in dendritic/spine extent obtained across cortical regions. Most apparent were substantial differences between BA4 and BA10: total dendritic length was 52% greater in BA4 than BA10, and dendritic spine number was 67% greater in BA4 than BA10. Neonatal patterns were compared to adult patterns, revealing that the relative regional pattern of dendritic complexity in the neonate was roughly the inverse of that established in the adult, with BA10 rather than BA4 being the most complex area in the adult. Overall, regional dendritic patterns suggest that the developmental time course of basilar dendritic systems is heterochronous and is more protracted for supramodal BA10 than for primary or unimodal regions (BA4, BA3-1-2, BA18).

Quantitative dendritic research has traditionally focused on only one cortical region at a time, which has severely limited appreciation of cortical variability. Fortunately, investigators have recently acknowledged that regional variation in pyramidal cell phenotype deserves attention because it appears to be strongly associated with the complexity of cortical circuitry, neural activity, and associated cognitive functions [Elston, 2000, 2003a]. Although such regional dendritic variation has been documented in adult primates [Elston and Rosa, 1997, 1998a, b; Jacobs et al., 2001], few if any studies have addressed such variation in human neonates. The present study thus examines the basilar dendritic systems of pyramidal neurons across hierarchically arranged regions of human infant neocortex. The purpose of the current investigation is twofold: (1) to document potential regional cortical differences in human neonates and (2) to compare infant regional dendritic patterns with established adult patterns.

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Although the neocortex has often been conceptualized as a relatively uniform structure, current perspectives underscore substantial regional heterogeneity across several cellular parameters, including dendritic/spine extent [Jacobs and Scheibel, 2002; Elston, 2002, 2003a]. Several comprehensive investigations indicate that nonhuman primate neocortex is characterized by a general caudal-rostral progression in dendritic/spine extent [Elston et al., 1996, 1999; Elston and Rosa, 1997, 1998a, b], with greatest complexity generally achieved in the prefrontal pyramidal neurons of Old World monkeys [Elston, 2000, 2003a]. Much the same obtains in humans. The basilar dendritic systems in Brodmann's area (BA) 18 pyramidal neurons appear to be less complex than those in BA10 [Jacobs et al., 1997]. Moreover, in an extensive examination of eight hierarchically arranged neocortical regions in humans, Jacobs et al. [2001] noted that basilar dendritic/spine systems in primary (BA3-1-2, BA4) and unimodal (BA22, BA44) regions were consistently less complex than in heteromodal (BA6β, BA39) and supramodal (BA10, BA11) areas. These findings in human and nonhuman primates suggest that cortical regions involved in the early stages of information processing (e.g., primary sensory areas) generally exhibit less complex dendritic/spine systems than those regions involved in the later, more integrative stages of cognitive processing (e.g., prefrontal cortex).

What remains unclear from research on regional variation is the relative course of ontogenetic development for cells across different cortical areas. Several lines of evidence suggest a heterochronous developmental pattern for cortical circuitry. In vivo neonatal neuroimaging indicates that human cortical maturation – as measured by sulcal-gyral development – begins in sensorimotor cortex, progresses towards the parietal-occipital region, and finally reaches the frontal lobes [Ruoss et al., 2001]. In terms of postnatal human synaptogenesis, synaptic density peaks around 3 months of age in auditory cortex [Huttenlocher and Dabholkar, 1997], 4–8 months in striate cortex [Huttenlocher and de Courten, 1987; Huttenlocher, 1990], and 1–2 years in frontal cortex [Huttenlocher, 1979]. Closely paralleling this synaptogenesis pattern is cortical metabolism [Jacobs et al., 1995], as measured by local cerebral metabolic rates for glucose (LCMRglc), which is initially low in neonatal cortex. Increases in postnatal LCMRglc are seen first in sensorimotor cortices, followed by increases in parietal, temporal, and occipital regions by 3 months of age, with prefrontal cortex becoming active at around 8 months [Chugani and Phelps, 1986; Chugani et al., 1987].

Juxtaposing the heterochronous ontogenesis of cortical circuitry with adult regional variability in dendritic systems underscores the dynamic nature of cortical development and suggests the following: those cortical regions that ultimately become the most dendritically complex in adults are initially less developed and require a longer maturational timeline. The present study investigates this concept by quantitatively examining the neonatal pattern of basilar dendritic systems in pyramidal neurons across four cortical regions, arranged along Benson's [1993] simplified hierarchical model of cortical processing: primary sensorimotor cortices (BA4, BA3-1-2), unimodal visual association cortex (BA18), and supramodal association cortex (BA10). Given that sensorimotor regions (BA4, BA3-1-2) mature relatively early ontogenetically and exhibit the highest metabolic levels in neonate cortex, dendritic systems in these two primary regions were expected to be most complex. The caudally situated BA18 was expected to exhibit an intermediate level of dendritic complexity, with the rostrally located, late-developing BA10 being characterized by the least complex dendritic systems. Finally, it was expected that the regional pattern of dendritic complexity in the neonate would be the inverse of that established in the adult [Jacobs et al., 2001].

Materials and Methods

Subjects

Tissue from 4 infants (mean age = 41 ± 40 days; 2 males, 2 females) was provided by Dr. Wes Tyson of Denver's Children's Hospital (table 1). All brains exhibited normal anatomical features, with no obvious signs of malformations in cortical or subcortical structures. Autopsy reports indicated no ischemic damage, edema, hemorrhage, or tissue softening in the central nervous system. Although one cannot completely rule out secondary neural sequellae of particular disease states during the agonal period, neuromorphological examination of the tissue revealed no obvious abnormalities. As such, all four infants were determined to be neurologically normal, and thus qualified for inclusion in the present study. Autolysis time averaged 21 ± 7 h. All samples were immersion fixed in a 10% buffered formalin solution for an average of 110 ± 71 days prior to staining. The research protocol was approved by The Colorado College Human Subjects Review Board (No. H94-004).

Tissue Selection and Preparation

Tissue samples (1 cm along the long axis of the gyrus) corresponding to the four BAs (BA4, BA3-1-2, BA18, BA10) were removed from the left hemisphere of each brain (fig. 1). These regions were chosen for several reasons: (1) they could be consistently located according to reliable landmarks in the neonate brain; (2) they had all been quantified in the adult brain using identical methodology [Jacobs et al., 1997, 2001], thus facilitating dendritic comparisons between the

Table 1. Subject summary

Subject	Autolysis time, h	Race	Cause of death
F3, 37 WG	21	Caucasian	sepsis; hepatic necrosis
F9	16	Asian	sepsis; congenital heart disease
M48, 40 WG	15	Caucasian	aspiration pneumonia secondary to neuromuscular disorder
M105	30	Caucasian	cardiac failure

Subjects are referred to by gender and by age in days. WG = Weeks of gestation (not known for all subjects).

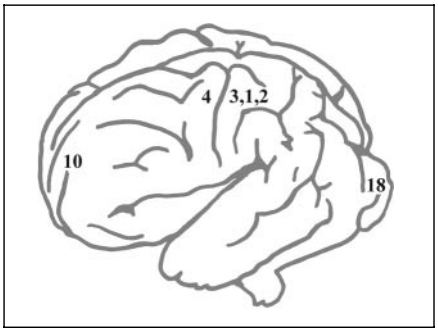


Fig. 1. Left hemisphere in the neonatal brain illustrating the four BAs from which tissue blocks were removed: motor (BA4), somatosensory (BA 3-1-2), visual association (BA18), and prefrontal (BA10) cortices.

neonate and the adult, and (3) they represented the three key domains (middle, caudal, and rostral cortical regions) in the developmental gradient outlined by Ruoss et al. [2001], and thus could capture potential ontogenetic patterns. The relative location and anatomical characteristics of these regions are briefly described below:

Brodmann's Areas 3-1-2 and 4. Areas 3-1-2 and 4 were removed from adjacent regions of the post- and precentral gyri, respectively (approximately 1 cm from the midline on the dorsolateral convexity).

Brodmann's Area 18. Area 18 was located on the lateral convexity, approximately 1cm superior to the inferior surface of the occipital lobe and 1.5 cm from the midline.

Brodmann's Area 10. Area 10 was removed superiorly from the frontal pole, approximately 1cm from the midline and 1.5 cm superior to the orbitomedial surface.

In accordance with previously established protocols [Jacobs et al., 1997, 2001], tissue blocks were stained using a modified rapid Golgi technique [Scheibel and Scheibel, 1978], and serially sectioned with a vibratome (120 μm). All tissue remained coded until quantification was completed.

Cell Selection and Dendritic/Spine Quantification

Although supragranular neurons have typically been used in previous adult studies of this nature [Jacobs et al., 1997, 2001], these cells were not quantified in the present study because (1) very few layer III cells stained, and (2) those that did stain adequately exhibited only very immature proximal dendrites, particularly in BA10 [cf. Mrzljak et al., 1988], thus making quantification of limited value. Neuronal impregnation was, however, relatively complete in lamina V. As such, 10 lamina V pyramidal cells per tissue block (N = 160) were randomly selected and traced based on previously established criteria [Jacobs et al., 1993, 2001]. All quantified neurons appeared fully impregnated and possessed relatively complete, uninterrupted basilar dendritic systems, consisting of at least three primary dendritic branches, and subsequent higher-order branching. No distinction was made between spine subtypes. Cells were quantified along x, y, and z coordinates on a Neurolucida computer system (version 3.16, Microbrightfield Inc., Willston, Vt., USA) interfaced with an Olympus BH-2 microscope under a planachromat 40× dry objective.

Independent and Dependent Variables

In the present study, cortical area (BA4, BA3-1-2, BA18, BA10) served as the independent variable. Five dependent measures characterized dendritic complexity: (1) total dendritic length refers to the summed length of dendritic segments; (2) mean segment length represents the mean length of dendritic segments; (3) dendritic segment count refers to the number of dendritic segments; (4) dendritic spine number refers to the sum of all spines on dendritic segments, and (5) dendritic spine density represents the average number of spines per micron of dendritic length.

It should be noted here that these measures are interrelated (e.g., total dendritic length is the product of mean segment length and dendritic segment count values), but each represents a slightly different characteristic of the dendritic envelope.

Statistical Analysis

The raw dendritic data set was aggregated by neuron (CELL). Separate analyses subsequently evaluated the effects of BAs (BRODMANN) on each of the five dependent measures by using a nested ANOVA design (PROC NESTED, SAS System for Windows, Cary, v. 8.0). In this model, CELL was nested within BRODMANN, each of which was nested within BRAIN. Briefly, this is ostensibly a nested, repeated measures design, whereby each dependent measure is afforded its own nested analysis, thereby increasing the ability to identify how much each independent variable contributes to the values found for the dependent measures. Because this design analyzed one dependent variable at a time, a Bonferroni-Dunn correction ($\alpha = 0.01$) was used to maintain an experimentwise α of 0.05.

Results

As predicted, dependent measures revealed the following pattern in terms of overall dendritic complexity among the four cortical regions: BA4>BA3-1-2, BA18>BA10. Photomicrographs of selected Golgi preparations from each cortical region indicate this general pat-

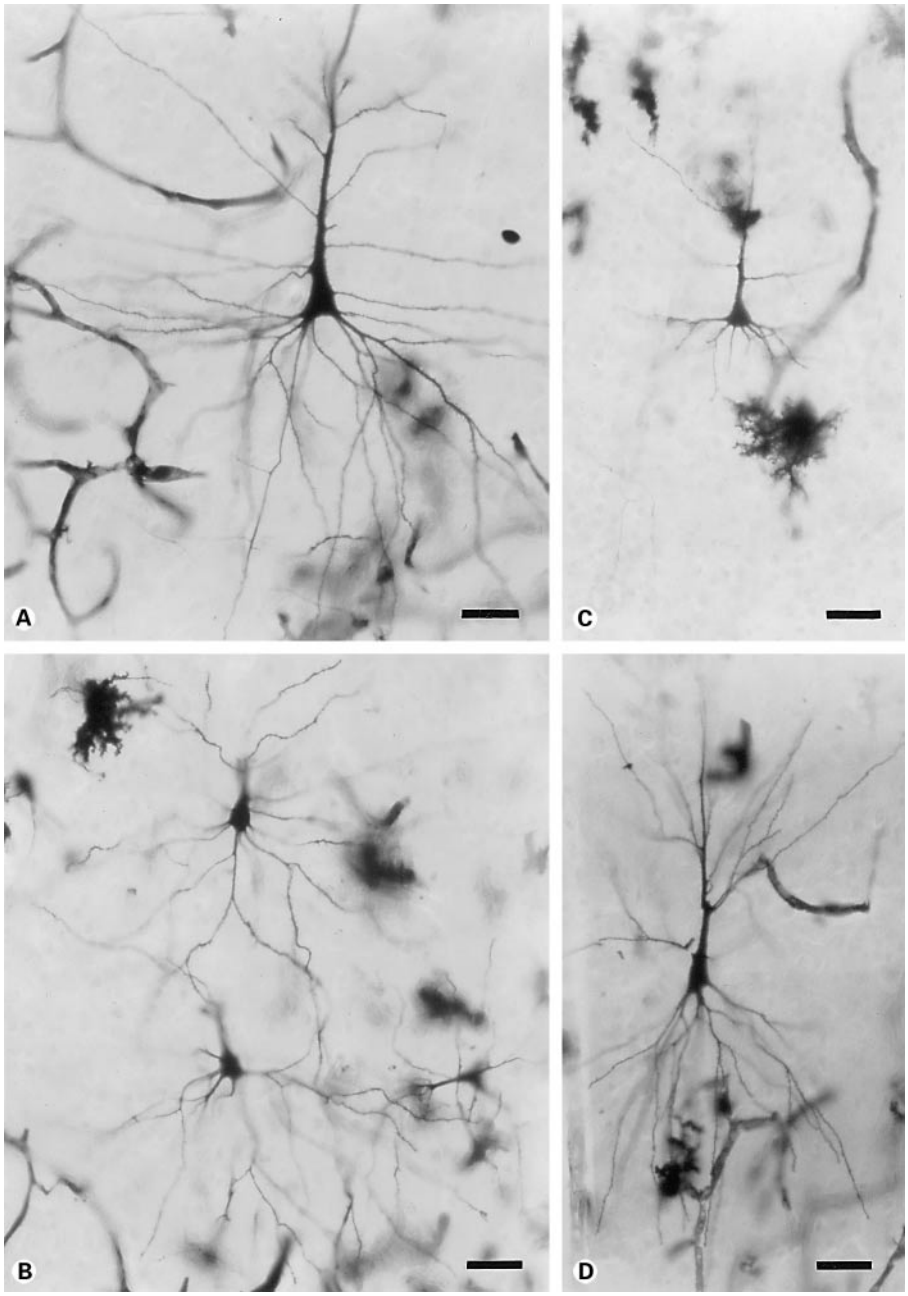
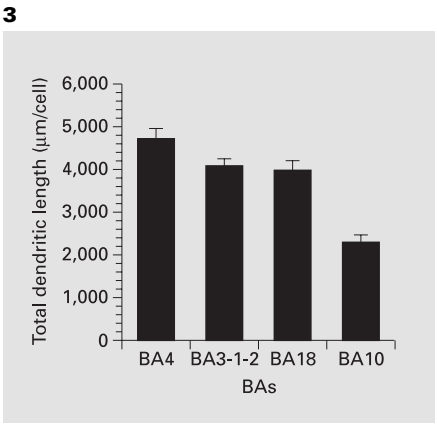


Fig. 2. Photomicrographs of rapid Golgi impregnated cells from neonatal neocortex, representing BA4 (**A**), BA3-1-2 (**B**), BA10 (**C**), and BA18 (**D**). All cells are photographed at the same magnification. Note the substantial size difference between BA4 and BA10 in terms of overall dendritic complexity. Scale bars = 50 μm.

tern along with the overall quality of the stain (fig. 2). Golgi-impregnated tissue did not exhibit the autolytic changes (e.g., irregular varicose enlargements, constriction of dendrites) described by Williams et al. [1978]. Pearson product correlations indicated no significant correlations among autolysis time (or subject age) and any of the dependent variables. Two measures were taken during data collection to minimize variability in the neuronal sampling procedure: (1) soma depth from the pial surface, and (2) soma size (table 2). These measures indicated a relatively homogeneous population of sampled infragranular pyramidal neurons.

Dendritic Complexity

Dendritic Length. Significant differences across BAs obtained for both total dendritic length [F(12, 144) = 8.29,



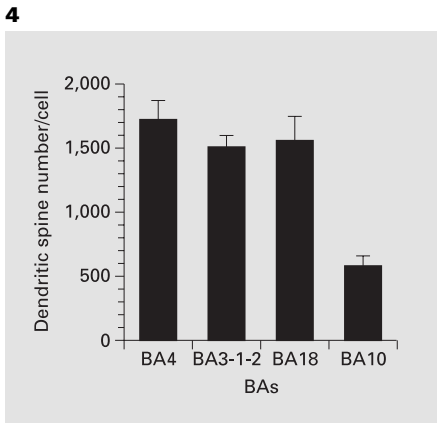


Fig. 3. Bar graph of the relative total dendritic length (μm) for each BA sampled in the neonate brain, arranged in a decreasing sequence: BA4 > BA3-1-2 > BA18 > BA10. Error bars represent SEM.

Fig. 4. Bar graph of the relative dendritic spine number for each BA sampled in the neonate brain. Note the decrease from BA4 to BA3-1-2/BA18 to BA10. Error bars represent SEM.

$p < 0.0001$] and mean segment length [$F(12, 144) = 10.20$, $p < 0.0001$]. Overall, total dendritic length was 52% greater in BA4 (4,733 μm/cell) than in BA10 (2,291 μm/cell). Figure 3 illustrates the pattern of dendritic complexity to be BA4>BA3-1-2>BA18>BA10. The same regional pattern obtained for mean segment length, which was 38% greater in BA4 (78 μm/cell) than in BA10 (48 μm/cell).

Dendritic Number. There were no significant differences for dendritic segment count, suggesting that the number of dendritic segments was similar across the 4 cortical regions.

Dendritic Spines. Significant differences emerged among BAs for both dendritic spine number [$F(12, 144) = 8.73$, $p < 0.0001$] and dendritic spine density [$F(12, 144) = 8.01$, $p < 0.0001$]. Dendritic spine number was 67% greater in BA4 (1,720 spines/cell) than in BA10 (573 spines/cell). Figure 4 illustrates the pattern of spine complexity to be BA4>BA18>BA3-1-2>BA10. For dendritic spine density, the pattern was slightly different: BA18 (0.32 spines/μm) exhibited the highest density value, which was 44% greater than that exhibited by BA10 (0.18 spines/μm).

Individual Variability in Dependent Measures

Although there was interindividual variability in dependent measures across cortical areas, there was also considerable uniformity. To illustrate this relative uniformity, the total dendritic length values of the four regions examined were ranked (1 = most complex; 4 = least complex) within each subject (table 3). The average total dendritic length ranking of BAs across the four subjects yielded the following: BA4 = 1.5, BA3-1-2 = 2.3, BA18 = 2.3, BA10 = 4. Moreover, BA10 was the least complex area across all subjects for all dependent measures.

Table 2. Sampled cell summary

	BA4	BA3-1-2	BA18	BA10
Soma size, μm^2	482 ± 138	378 ± 147	380 ± 97	318 ± 139
Soma depth, μm	1,927 ± 579	1,658 ± 527	1,507 ± 364	1,564 ± 744

Values are presented as mean ± SD.

Table 3. Rank ordering of total dendritic length across BAs for each subject

Subject	BA4	BA3-1-2	BA18	BA10
F3	3	2	1	4
F9	1	2	3	4
M48	1	2	3	4
M105	1	3	2	4
Mean	1.5	2.3	2.3	4.0

Rankings as follows: 1 = most complex region; 4 = least complex region.

Subjects are referred to by gender and by age in days.

Discussion

The present investigation revealed significant differences in dendritic/spine extent among hierarchically arranged cortical regions of the neonatal human brain. Although the exact ordering of individual BAs depended somewhat on the particular aspect of the dendritic tree examined (as illustrated in fig. 3, 4), clear patterns did

emerge. In general, dendritic/spine systems were most complex in BA4 and least complex in BA10. Before discussing these results in detail, however, methodological issues need to be addressed.

Methodological Considerations

The limitations of human quantitative research and the Golgi methods have been extensively documented elsewhere, and will not be repeated here [Schadé et al., 1964; Williams et al., 1978; de Ruiter, 1983; Mrzljak et al., 1992; Jacobs et al., 1993, 1997, 2001]. As has been noted in quantitative neuromorphological studies in adults [Jacobs et al., 1997], one methodological issue (e.g., 120-μm-thick sections quantified under light microscopy) is that the present results are probably underestimations of actual dendritic/spine extent, particularly in the regions with the most extensive dendritic systems (e.g., in the neonate, BA4). Thus, the obtained regional differences in the present study may actually be greater than reported here.

In addition, the primary limitation of the present study is the small sample size, which is not unusual for quantitative dendritic research in primates [cf. Schulz et al., 1992; Koenderink and Uylings, 1996; Elston and Rosa, 1998a, b; Elston and Rockland, 2002]. It should be noted, however, that each subject in the present sample serves as his/her own control, and thus provides a relatively stable basis for inter-regional comparisons. In addition, the present population of 160 neurons does provide a sufficient sample for tentative conclusions, although a much larger, cross-sectional sample would be more definitive.

Regional Differences in Neonatal Cortex

Qualitatively, the stained pyramidal cells in the present study generally resembled those described in the human developmental literature [Marín-Padilla, 1970, 1992; Takashima et al., 1980; Mrzljak et al., 1988, 1990; Cordero et al., 1993]. Sampled pyramidal neurons exhibited relatively complete arrays of primary basilar dendrites, with rudimentary distal segments in place. In addition, layer V pyramidal neurons were clearly more differentiated than their supragranular counterparts, particularly in BA10. Quantitatively, the observed pattern in dendritic/spine complexity (BA4>BA3-1-2, BA18>BA10) is consistent with the heterochronous developmental pattern that characterizes regional cortical variation [Sauer et al., 1983; Huttenlocher and Dabholkar, 1997]. The relative complexity of BA4 vis-à-vis the other cortical regions was expected insofar as (1) both somatosensory and motor areas appear to mature relatively early [Ruoss et al., 2001], and (2) BA4 is more richly interconnected than BA3-1-2 [Jones et al., 1978]. It should be noted, however, that it is doubtful whether primary motor cortex can be equated with primary sensory regions [Jacobs et al., 2001] because BA4 uniquely contains disproportionately extensive layer V pyramidal neurons [Marín-Padilla, 1970], a characteristic that undoubtedly contributed to the overall complexity of BA4 in the current study.

The dendritic/spine systems of BA3-1-2 and BA18 were generally less complex than those in BA4. Because the proximal dendrites in BA3-1-2 are essential to the intrinsic corticocortical connections of this region [Porter, 1997], these pyramidal neurons appear to mature relatively quickly and are likely crucial to the relatively early functional maturity of BA3-1-2 [Chugani et al., 1987]. Although visual cortical regions may mature somewhat later than BA3-1-2 in terms of sulcal-gyral development [Ruoss et al., 2001], visual cortex nevertheless matures earlier ontogenetically than does the overall brain in terms of laminar development, functional ability, synaptogenesis, and local metabolic rates [Sauer et al., 1983; Chugani and Phelps, 1986; Huttenlocher, 1990]. Thus, it is understandable that BA3-1-2 and BA18 were similar in terms of their dendritic/spine extent in the present study – both regions become functionally active early in neonatal development.

In contrast, early maturation of BA10, which is involved in transmodal integration of a broad spectrum of information [Fuster, 1973; González-Burgos et al., 2000], is probably not as crucial for the neonate. In fact, all indicators – gross anatomy [Ruoss et al., 2001], synaptogenesis [Huttenlocher, 1979], myelogenesis [Yakovlev and Lecours, 1967], cortical metabolism [Chugani et al., 1987], function [Fuster, 1989; Diamond, 1991] – suggest that the prefrontal lobe is the last to mature ontogenetically and that it has a protracted developmental time course. Layer V pyramidal neurons, which primarily form subcortical connections, appear to undergo continued restructuring during the early postnatal period into the second year of life [Mrzljak et al., 1988, 1990, 1992]. Indeed, dendritic arborization in frontal cortex has been shown to develop more slowly than in visual cortex or the hippocampus [Paldino and Purpura, 1979; Becker et al., 1984; Webb et al., 2001]. As such, it is not surprising that BA10 consistently exhibited the least complex dendritic/spines systems of all regions in the present investigation.

Regional Dendritic Comparison of Infant and Adult Neocortex: Relative Differences

The heterochronous pattern of dendritic development in humans clearly begins in utero, and continues well into

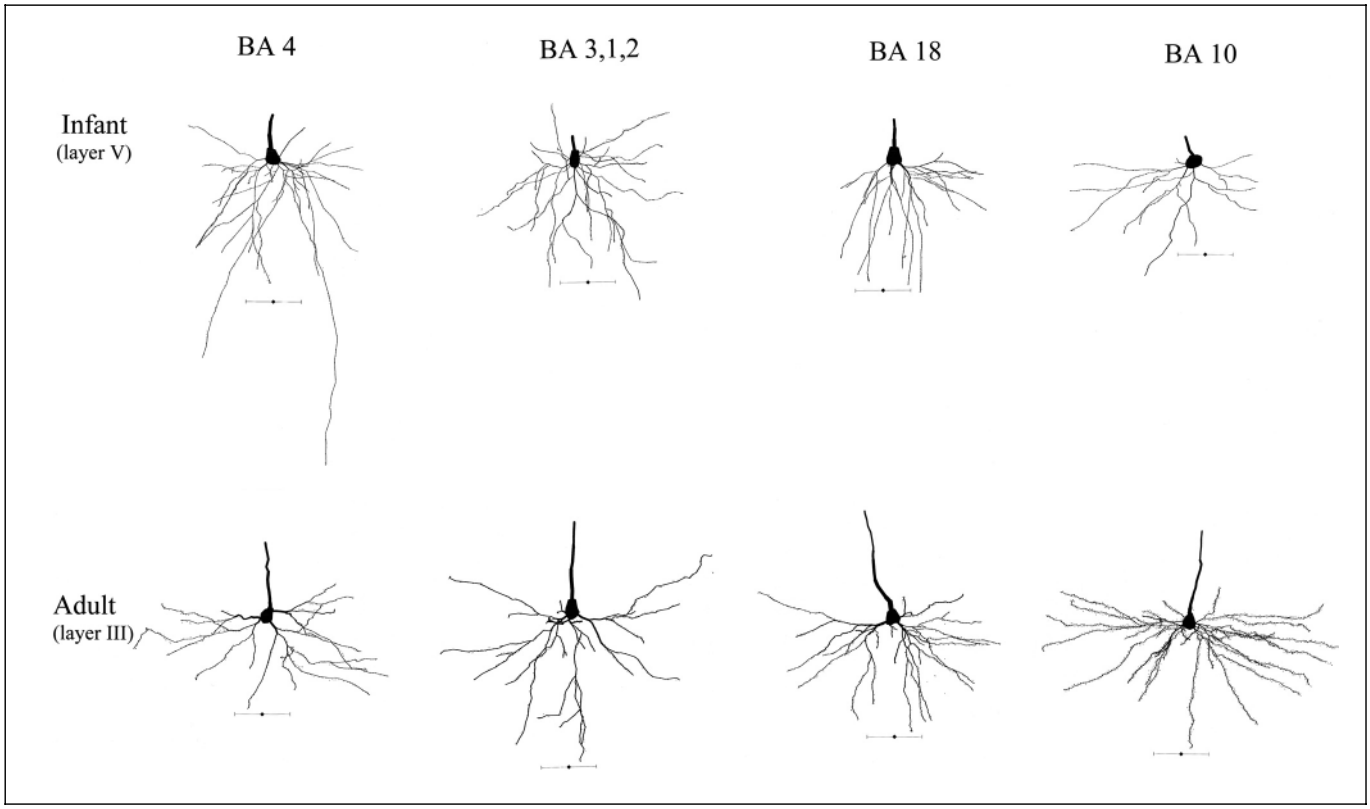


Fig. 5. Sample tracings of pyramidal cells from the four BAs examined in the present study. In the top row, infant layer V basilar dendritic systems are represented from most complex (BA4) to least complex (BA10). In the bottom row, adult tracings [from Jacobs et al., 1997, 2001] of layer III pyramidal neurons are presented in the same order as the infant. In the adult, however, BA10 exhibits a more complex dendritic array than any of the other three regions. The relative pattern of dendritic complexity is thus roughly inverted between the infant and the adult brain. Scale bars = 100 μm.

adulthood [Jacobs et al.,1997]. However, the present findings indicate that early cortical maturation does not necessarily predict ultimate dendritic complexity. To illustrate this possibility, the present results in neonates are compared with the regional dendritic patterns observed in adults. However, only relative differences in dendritic/spine patterns among regions are considered here because the adult studies examined layer III rather than layer V pyramidal neurons. Thus, no direct comparisons are made between any one region (e.g., BA4) in adults and infants; instead, the emphasis is on the pattern among regions within infants, and the pattern among regions within adults. Other than the laminar sampling difference, the adult studies followed the same methodology as the present investigation, and thus are subject to the same limitations. Dendritic values for adult BA4, BA3-1-2, and BA10 were based on a total of 100 cells/area, sampled from 10 subjects averaging 30 ± 17 years of age [Jacobs et al., 2001]; values for adult BA18 were based on a total of 260 cells, sampled from 26 subjects averaging 57 ± 22 years of age [Jacobs et al., 1997].

Certainly, comparing layer III and V pyramidal neurons is far from ideal. Nevertheless, it should be noted that, given the inside-out development of neocortex [Marín-Padilla, 1970], what seems to vary between neurons in layer III and layer V is primarily the time course of dendritic growth rather than any qualitative difference [Schadé and van Groenigen, 1961; Semenova et al., 1990]. In fact, the general developmental pattern in layer III and V pyramidal neurons is similar [Mrzljak et al., 1992]. The main difference is that layer V pyramidal neurons, from which efferent fibers originate, mature earlier than their layer III counterparts, which are more concerned with corticocortical processing. In human visual

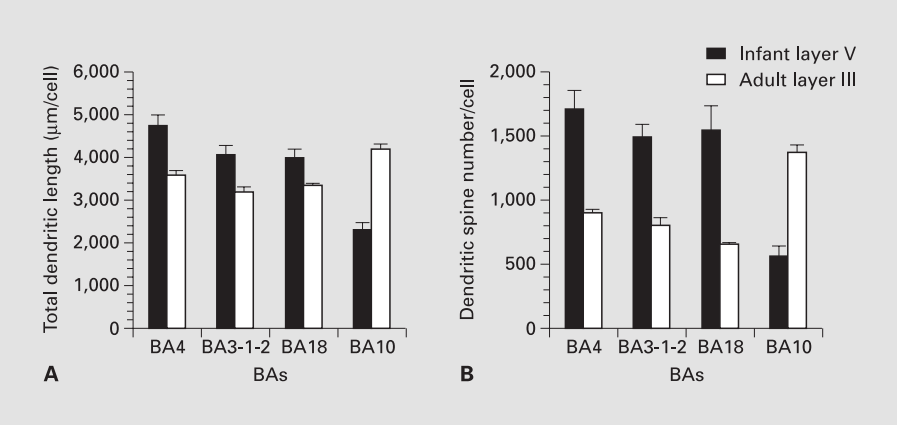


Fig. 6. Bar graphs representing total dendritic length (μm) (**A**) and dendritic spine number (**B**) for each BA in the present study. The relative pattern across regions is highlighted between infant layer V pyramidal neurons and adult layer III pyramidal cells [from Jacobs et al., 1997, 2001]. Comparison within regions for adults and infants is not warranted because they represent different cellular populations. For both measures, infant values decrease from BA4 to BA10. In contrast, adult BA10 values are higher than those for all other adult regions. Error bars represent SEM.

cortex, for example, layer III pyramidal neurons exhibit only about 35% of their maximal dendritic extent at birth [Becker et al., 1984]. In contrast, layer V cells exhibit about 55% of their total length. Thus, the following relative rather than absolute regional comparisons should prove illustrative with regards to the heterochronous path of dendritic development.

Sampled cell tracings representing the regional patterns in dendritic extent between neonates and adults are provided in figure 5. Layer V pyramidal neurons in the neonate indicate a clear decrease in dendritic complexity from BA4 to BA10. In contrast, layer III pyramidal neurons in adults exhibit a clear increase in dendritic complexity from BA4 to BA10. Quantitative comparisons of these relative patterns are provided in figure 6, which graphically represents these dendritic patterns among infants and adults for both total dendritic length and dendritic spine number. In neonates, there is a decrease in dendritic/spine extent from BA4 to BA3-1-2/BA18 to BA10. In adults, however, total dendritic length (fig. 6A) and dendritic spine number (fig. 6B) are both highest in BA10, and substantially lower in the other three regions. Indeed, extensive research on the visual [Elston et al., 1996; Elston and Rosa, 1997, 1998b; Elston, 2003b], and sensorimotor [Jacobs et al., 2001; Elston and Rockland, 2002] systems confirms that cortical regions higher in the processing hierarchy (e.g., prefrontal cortex) exhibit more complex dendritic/spine systems [Elston and Rosa, 1998a; Elston et al., 2001; Jacobs et al., 2001; Elston, 2003a]. The two opposing dendritic/spine patterns between human infants and adults suggest that the developmental time course for pyramidal neurons varies across cortical regions according to the ultimate functional complexity of the region.

In a simplified hierarchical framework [cf. Mountcastle, 1995; Jacobs et al., 2001], such as proposed by Benson [1993] and Mesulam [1998], a somewhat heterochronous developmental pattern is expected because cortical regions higher along the sensory-fugal gradient require the relative functional maturity of regions involved in the initial stages of information processing [Semenova et al., 1990; Webb et al., 2001]. Neuronal differentiation, as reflected by increases in basilar dendritic field size, is at least partially determined by the ingrowth of afferent fibers and the outgrowth of efferent connections [Kostovic and Goldman-Rakic, 1983; Mrzljak et al., 1988, 1992], both of which appear to develop earlier ontogenetically in primary cortical areas. The development of such cortical circuitry is reflected by changes in synaptogenesis [Huttenlocher, 1979, 1990; Huttenlocher and Dabholkar, 1997; Huttenlocher and de Courten, 1987], myelination [Gibson, 1991], metabolic rates [Chugani et al., 1987], intrinsic axonal clusters [Amir et al., 1993; Lund et al., 1993], and dendritic proliferation [Michel and Garey, 1984; Mrzljak et al., 1988, 1992; Semenova et al., 1990; Koenderink et al., 1994; Koenderink and Uylings, 1995]. All of these indicators appear to peak much earlier ontogenetically in primary cortical areas than in associative prefrontal regions. Postnatal cortical reorganization thus appears to precede heterochronously from primary cortical areas, which are more complex in the neonatal period, to supramodal regions, which achieve highest levels of dendritic complexity in adults.

The present results provide further support for the idea that phenotypic variation in pyramidal neurons appears to underlie intrinsic inter-areal cortical differences [Elston and Rockland, 2002; Elston, 2003a]. Specifically, the present developmental perspective suggests that those

cortical regions exhibiting more complex pyramidal neurons and their associated circuitry in the adult are relatively immature at birth, develop more slowly than primary cortical regions, but ultimately exhibit more complex intrinsic circuitry. A potential reason for this relatively prolonged development could be that pyramidal cells in prefrontal regions develop more complex dendritic arborizations as more intricate, long-distance corticocortical connections are formed [Duan et al., 2002]. Given this delayed development of higher order cortices, it is also conceivable that neurons in these regions are somewhat more open than primary regions to epigenetic influences as they form corticocortical connections. Prefrontal cortex such as dorsolateral BA10, for example, integrates diverse, previously processed sensory information from parietal, temporal, and occipital association areas [Jacobson and Trojanowski, 1977; Preuss and Goldman-Rakic, 1991], and displays the type of persistent neural activity [Elston, 2003a] necessary to orchestrate top-down control of memory and attention mechanisms [Fuster, 1973, 2000]. A relatively long developmental time-course, as suggested in the current results, seems to be required to develop the necessary long-distance circuitry [McGuire et al., 1991; Melchitzky et al., 1998; Duan et al., 2002] that facilitates such an orchestration of other cortical regions.

The present results leave two issues unresolved, however. First, the extent to which developmentally transient neuronal populations (i.e., subplate and marginal zone cells) shape the emerging dendritic/spine systems of pyramidal neurons remains unknown. Although these transient populations are present in large numbers during development [Chun et al., 1987], and although they promote the survival of immature cortical neurons [McConnell et al., 1994; Finney et al., 1998], it is not known if they contribute to the regional dendritic variability observed in the present study. Second, it is not clear if the postulated heterochronous dendritic development in humans also obtains in nonhuman primates. Certainly, adult New and Old World monkeys also exhibit considerable, and clearly delineated cortical heterogeneity along several parameters [Elston, 2002], but the ontogenetic time-course behind this inter-areal variability remains unspecified, particularly since the developmental time period is substantially compressed in monkeys. It has, in fact, been suggested that transient synaptic overproduction in monkeys occurs concurrently in different cortical areas [Rakic et al., 1986], which would argue against a heterochronous developmental pattern. Nevertheless, developmental research with a finer time resolution might reveal subtle differences in the ontogenesis of cortical regions [Jacobs et al., 1995]. To this end, developmental nonhuman primate investigations with greater temporal resolution seem warranted to elucidate the heterochronous pattern suggested by human cortical research.

Conclusion

The present quantitative investigation of regional dendritic variation in the human neonate complements existing data on inter-areal morphological differences in adult neocortex. Despite the small sample size, current results revealed clear and consistent regional dendritic/spine differences across four hierarchically arranged cortical regions in the neonate: BA4 > BA3-1-2, BA18 > BA10. This pattern is considerably different than the pattern observed in adults, where BA10 is substantially more complex than all other regions. Finally, the present perspective suggests a heterochronous development pattern, whereby those cortical regions exhibiting more complex pyramidal neurons in the adult are relatively immature at birth, develop more slowly than primary cortical regions, but ultimately exhibit more complex dendritic/spine systems.

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