Evo-Devo and the Primate Isocortex: The Central Organizing Role of Intrinsic Gradients of Neurogenesis

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Abstract

Spatial gradients in the initiation and termination of basic processes, such as cytogenesis, cell-type specification and dendritic maturation, are ubiquitous in developing nervous systems. Such gradients can produce a niche adaptation in a particular species. For example, the high density of photoreceptors and neurons in the 'area centralis' of some vertebrate retinas result from the early maturation of its center relative to its periphery. Across species, regularities in allometric scaling of brain regions can derive from conserved spatial gradients: longer neurogenesis in the alar versus the basal plate of the neural tube is associated with relatively greater expansion of alar plate derivatives in larger brains. We describe gradients of neurogenesis within the isocortex and their effects on adult cytoarchitecture within and across species. Longer duration of neurogenesis in the caudal isocortex is associated with increased neuron number and density per column relative to the rostral isocortex. Later-maturing features of single neurons, such as soma size and dendritic spine numbers reflect this gradient. Considering rodents and primates, the longer the duration of isocortical neurogenesis in each species, the greater the rostral-to-caudal difference in neuron number and density per column. Extended developmental duration produces substantial, predictable changes in the architecture of the isocortex in larger brains, and presumably a progressively changed functional organization, the properties of which we do not yet fully understand. Many features of isocortical architecture previously viewed as species- or niche-specific adaptations can now be integrated as the natural outcomes of spatio-temporal gradients that are deployed in larger brains.

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Introduction

David Marr [1982] famously argued that with an appropriate algorithm and adequate time, any computation could be performed on any hardware assembly, from Tinker-Toy engines to transistors. Marr's claim may be true in an abstract computational sense, but we will counterclaim that the nature of the 'hardware assembly' de-

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pends on the time it takes to assemble it. In particular, spatiotemporal gradients in corticogenesis and maturation [Ragsdale and Grove, 2001; Rakic, 2002; Sansom and Livesey, 2009] produce different architectures in small and rapidly developing brains compared to large, slowly developing ones. The field of evolution and development is concerned with the developmental programs that are conserved and those that are modified to produce diversity in brains [Striedter, 2005; Wagner et al., 2007; Shubin et al., 2009]. The desired computational outcome, the construction materials, toolbox, construction time and budget must be considered in relation to its development. This is the 'devo' aspect of an evo-devo account of the brain; the 'evo' component further specifies that plans employed for construction can only be small modifications of plans from previously existing devices.

The basic structure of the vertebrate brain and the general pattern of its development are quite conservative across species despite diverse behavioral repertoires [Puelles and Rubenstein, 2003; Puelles et al., 2013]. Whether this conservation is best viewed as the result of developmental constraints [Gould, 1980], or as an optimization of a robust and evolvable developmental plan [Kirschner and Gerhart, 2005], awaits a better understanding of the possible diversity in computational brain architectures. Here, we focus on the evolution of the human brain, and its most imposing structure, the isocortex.

The isocortex varies widely in size in mammals, and humans have a large isocortex compared with many other mammals, though not the largest [Stephan et al., 1981; Eriksen and Pakkenberg, 2007]. Brain size, the number of its subdivisions (e.g. cortical areas) and the duration to produce it are extremely tightly correlated [Passingham, 1985; Finlay and Darlington, 1995; Clancy et al., 2001; Finlay and Brodsky, 2006; Workman et al., 2013]. Thus, the study of the isocortex, the neural structure with the greatest variation in volume across species, is also the study of a structure with the greatest variation in the duration of its production [Finlay and Darlington, 1995; Workman et al., 2013]. We will describe the developmental mechanisms that give rise to variation in neurons and cellular architecture across the isocortex and across species.

In addition to the overall timing of developmental schedules between large and small brains, spatiotemporal gradients across and within brain subdivisions appear in nearly all aspects of neural development, including neurogenesis, maturation of cellular processes, synaptogenesis and myelination [Cooper and Rakic, 1983; Mc-

Sherry, 1984; McSherry and Smart, 1986; Cavalcante et al., 1991; Rapaport et al., 1996; Workman et al., 2013]. Cataloguing all of these gradients would be laborious and uninformative given their ubiquity. Instead, we concentrate on examples where the spatiotemporal gradients in developmental processes have likely or known functional consequences, with attention to how such gradients change in species with varying overall developmental duration.

Many studies of neurogenesis in rodents show considerable overlap in neuron production within neural subdivisions, such as thalamic nuclei and their subdivisions, or cortical layers [e.g. Bayer and Altman, 1991] while comparable studies in carnivores and primates show more temporally distinct patterns [McSherry, 1984; McSherry and Smart, 1986; Rakic, 2002]. What is the nature of greater 'temporal distinction'? In an earlier work, Finlay et al. [1998] considered an organizational feature that could be called 'event dissociability' for distributing embryological events into short or long durations [Darlington et al., 1999]. Suppose neural regions A, B and C are produced consecutively in corresponding bouts of neurogenesis. If the same (scaled-up) structures are produced in a larger brain, do these consecutive 'bouts' and the potential intervals between them scale in the same way? Bouts of a process (e.g. neurogenesis) might hold together because of an internal mechanistic requirement, while intervals between bouts might lengthen. Consider the difference between stretching an elastic necklace with beads a, b and c, versus a uniform elastic band with the simple divisions a, b and c. The answer is quite clear: for any process we could designate, there was no difference between 'bouts' and 'intervals' at any duration of development. For homologous units, such as the 'lateral geniculate nucleus' (LGN), 'striate cortex' or 'layer IV of striate cortex', beginnings and ends overlapped as much for species with short and long developmental durations. A rhesus macaque does not, for example, generate the LGN and later generate the cortex, while the rat generates both simultaneously. Rather, in the rat and rhesus macaque, the LGN and layers V/VI of the striate cortex are generated roughly synchronously, but the rhesus monkey generates these for a proportionately longer time.

Spatiotemporal gradients emerge over large structures, or structural subdivisions in larger brains, such as the layers of the LGN, or the numerous sublaminae of layer IV in the primate striate cortex. For instance, in monkeys, there is a center-to-peripheral gradient in neurogenesis timing in the developing retina and a rostro-

caudal (also known as anterior to posterior) gradient in neurogenesis timing in the presumptive isocortex [Rakic, 2002; Finlay, 2008], which is less pronounced in rodents [Polleux et al., 1997; Nowakowski et al., 2002; Finlay et al., 2005; Suter et al., 2007]. Whether the emergence of spatiotemporal gradients within structures is latent in the mechanism that produces a given structure in a small brain and is simply revealed in a larger brain, or whether spatiotemporal gradients evolve independently of other spatiotemporal gradients does not appear to have a specific answer. Evidence for both possibilities exists. The relative uniformity of the cortical gradients that we will discuss as they emerge in various mammalian lineages suggests it is a latent feature. In the retina, by contrast, the particular spatiotemporal gradient in neurogenesis is often related to species-specific retinal specializations, like a 'streak' or 'area centralis' [Finlay, 2008; Dyer et al., 2009]. These gradients are employed to produce differences in neuron number, cell types and arrangement in larger brains, which are not as salient in their smaller homologues [Sherwood et al., 2006, 2007; Charvet et al., 2013].

We will describe a spatiotemporal gradient in neuron production in the isocortex. Specifically, there is a rostro-caudal (also known as anterior to posterior) gradient in neurogenesis timing across the presumptive isocortex. Neurons undergo terminal neurogenesis earliest in the rostral pole and last in the caudal pole [Rakic, 1974, 2002]. The greatest difference in neurogenesis timing between species is observed within its caudal pole. We argue that the rostro-caudal gradient in neurogenesis timing produces pronounced and predictable variation in neuron numbers across the cortex and is most pronounced in largest brains [Charvet et al., 2013]. This amplification of hierarchy along the 'feed-forward' versus 'feed-back', caudal-to-rostral dimension and the resulting severe reduction in the dimensionality of representations as they cascade across the occipito-parietal to frontal cortex provides an important clue to understand how larger cortices process information across their axes.

Examples of Spatiotemporal Gradients

Through the brain, neurogenetic schedules vary across the rostro-caudal axis of the central nervous system and within neural segments. The central nervous system can be subdivided into segments [Bergquist and Källén, 1954]. These segments are called rhombomeres in the rhombencephalon and prosomeres in the prosencepha-

lon [Rubenstein et al., 1994; Puelles et al., 2013]. Each of these segmental subdivisions gives rise to various cell types and these segmental subdivisions vary in their developmental schedule. Across the central nervous system, terminal neurogenesis has a tendency to occur latest in the most rostral and lateral segmental divisions (e.g. isocortex) and earliest in the most caudal and basal divisions [Finlay et al., 1998; Charvet et al., 2011; Workman et al., 2013]. The protracted timing of neurogenesis in the most rostral and lateral divisions of the central nervous system entails that cells undergo more rounds of cell divisions and expand disproportionately relative to regions that undergo terminal neurogenesis earlier [Finlay and Darlington, 1995; Workman et al., 2013]. The evolutionary reflection of this pattern is that alar regions associated with the cerebellum, midbrain, dorsal thalamus and telencephalon enlarge independently and repeatedly in vertebrates.

Within subdivisions, spatiotemporal gradients may emerge within larger structures, as outlined earlier. In the retina, there is a specific birth order in the cell types that comprise it. Ganglion cells are produced first, followed by cones and rods [La Vail et al., 1991; Rapaport et al., 1996]. Most retinas also have some spatiotemporal order from central to peripheral in offset of neurogenesis. In the large retinas of carnivores and primates, these gradients of cell type and retinal location can be so pronounced that the production of one cell class can be concluded in one location, while continuing in others, but this is much less so in rodents [Henderson et al., 1988; Wikler et al., 1989; La Vail et al., 1991; Rapaport et al., 1996; Reese et al., 1996]. For instance, retinal neurogenesis lasts for more than 80 days in the rhesus monkey [La Vail et al., 1991] but only lasts approximately 30 days in the rat [Rapaport et al., 2004]. At the end of retinal neurogenesis in the monkey, no neurons or photoreceptors are being generated in the central retina while neurogenesis in the peripheral retina is ongoing; in the rat, all cell types are generated at all locations at all times, with only a modest center-to-peripheral gradient. These spatiotemporal variations can be employed to produce species-typical retinal specializations. For instance, variation in the spatiotemporal axes of neurogenesis in the retina accounts for increased photoreceptors in the visual streak of rabbits [Robinson et al., 1989], the area centralis of cats [Robinson, 1987] and the fovea in primates [reviewed in Finlay et al., 2005, 2008]. Spatiotemporal gradients in retinal neurogenesis timing are also observed between species adapted for diurnal and nocturnal activity patterns [Finlay, 2008; Dyer et al., 2009].

Finally, across sensory systems, 'early developing portions of receptor sheets may gain more than their share of territory in sensory maps' [Catania, 2001; Kaas and Catania, 2002] and become a mechanism of sensory specializations. The early development of barrel fields representing rodent whiskers [McCandlish et al., 1993], the representation of the somatosensory fovea in the star-nosed mole [Catania and Kaas, 1997] and the preferential representation of the fovea in the visual cortex of primates [Finlay et al., 2005] are examples of this phenomenon. Not all specializations develop in this fashion. A notable exception is the acoustic foveae of bats [Rubsamen and Schafer, 1990].

Gradients of Neurogenesis in the Isocortex

Spatiotemporal gradients in neurogenesis timing are observed in the presumptive isocortex. In some species, the difference in terminal neurogenesis between the rostral and caudal pole varies at most by a few days, whereas in other species the difference in terminal neurogenesis occurs for over more than 2 weeks. For instance, in mice, neurogenesis starts around embryonic day (ED) 11 throughout the presumptive isocortex and terminal neurogenesis in the rostral and caudal pole lasts for approximately 6–8 days [Polleux et al., 1997]. In the rhesus monkey *(Macaca mulatta)*, neurons exit the cell cycle on approximately ED 38 throughout the isocortex. Neurogenesis in the rostral pole terminates on approximately ED 80, but neurogenesis in the caudal pole terminates on ED 102 [Rakic, 1974, 2002]. A prolongation in the duration of neurogenesis in the caudal pole entails extending the duration in which cells proliferate and a delay in the switch from proliferative symmetrical to asymmetrical cell divisions [Dehay and Kennedy, 2007; Charvet and Striedter, 2011]. Delaying cell cycle exit also entails delaying the decline in the cell cycle rate [Takahashi et al., 1995; Charvet and Striedter, 2008], which implies cells cycle faster for longer and amplifies the difference in founder populations across the developing isocortical axes. Delays in cell cycle exit and delays in the decline in the cell cycle rate both exponentially expand the number of proliferative cells and cause a disproportionate expansion of neurons in adulthood. Although the cell cycle rate in the presumptive isocortex is approximately three times longer in the rhesus monkey (cell cycle rate = 23 h) compared with mice (cell cycle rate = 8 h) by the time isocortical neurogenesis begins [Takahashi et al., 1995; Kornack and Rakic, 1998], proliferat-

ing cells in the caudal pole of the rhesus monkey have 20 more days to undergo cell divisions compared with those in the rostral pole.

As developmental schedules lengthen, events that occur late occur disproportionately later than events that occur earlier [Finlay and Darlington, 1995; Clancy et al., 2001; Workman et al., 2013]. A model that translates developmental timing can be used to determine how the length of overall developmental schedules covaries with the spatiotemporal gradients of neurogenesis. The model predicts developmental timing across species with high accuracy (r = 0.9929). In this model, the timing of 271 neural events in 18 mammalian species is regressed against event scores, where each neural event is ranked according to its sequence in development and ranges from 0 to 1 [Workman et al., 2013]. An event with a value close to 0 represents an event that occurs relatively earlier than most other events, and an event with a value close to 1 represents an event that occurs relatively later than most other events in the dataset. Overall developmental duration is defined as the range of developmental duration in days of each species by subtracting the corresponding y value when the event scale is 1 and when it is 0. We previously predicted the timing of terminal neurogenesis in layers II/III of the primary somatosensory cortex and in the primary visual cortex [Workman et al., 2013]. Neurogenesis timing in the primary somatosensory cortex was chosen because it is the most rostrally selected region within the isocortex in our dataset. Although the primary somatosensory cortex is not located at the rostral pole, it is situated rostrally enough that it may be used to contrast the difference in isocortical neurogenesis timing between rostral and caudal regions across species (fig. 1). Selecting a region that is more rostrally located than the primary somatosensory cortex would likely amplify the observed difference in neurogenesis duration between the rostral and caudal poles.

Developmental duration plotted against the difference in duration between terminal neurogenesis in the somatosensory cortex (rostrally) and the primary visual cortex (the caudal pole) increases as overall developmental schedules lengthen (fig. 1). That is, a lengthened overall developmental schedule implies a greater difference in neurogenesis duration between the rostral and caudal pole of the isocortex and an exponential increase in neurons in the caudal pole. There is variation in the spatiotemporal gradients of neurogenesis across species where spatiotemporal gradients become more prominent in species with longer developmental schedules.

Fig. 1. The difference in terminal neurogenesis between the anterior (i.e. primary somatosensory cortex, S1) and posterior cortex (i.e. primary visual cortex, V1) is regressed against the natural-logged values (ln) of developmental duration in eutherian mammalian species. The translating time model predicts that, as overall developmental schedules lengthen, the difference in the duration of terminal neurogenesis across the presumptive isocortical axis increases.
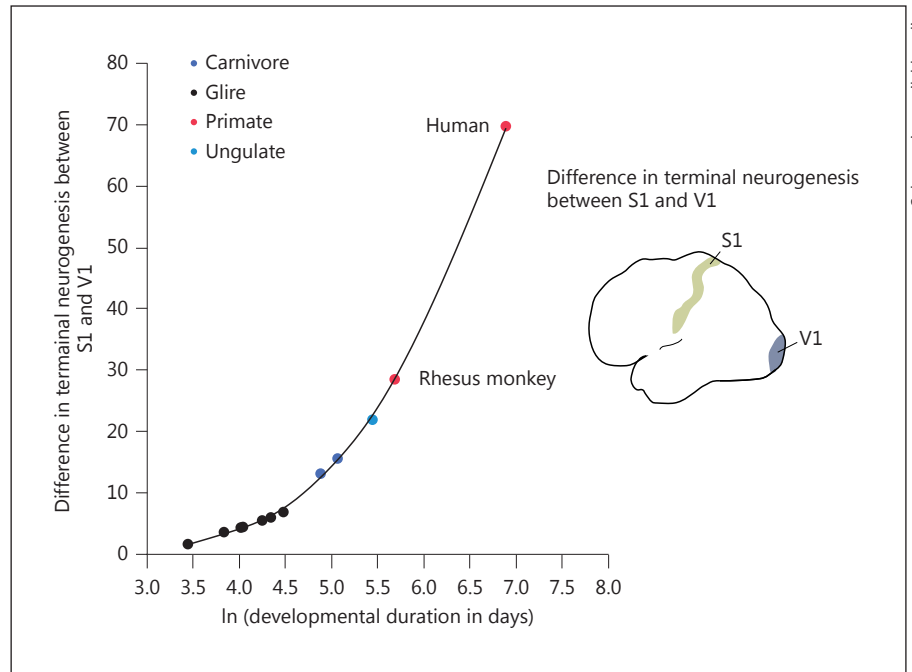
Influences of Developmental Gradients on Neuron Numbers

In some species with short developmental schedules and small spatiotemporal gradients in isocortical neurogenesis duration, neurons per unit of cortical surface area vary relatively little across the isocortex. For instance, hamsters develop for a relatively short period of time and the difference in neurons per unit of cortical surface area between the rostral and caudal pole is small (fig. 2) [Charvet et al., 2013; Workman et al., 2013]. In species with relatively prolonged developmental schedules and large differences in neurogenesis duration between the rostral and caudal pole, such as primates and carnivores, there is extensive variation in neurons per unit of cortical surface area (fig. 2) [Beaulieu and Colonnier, 1989; Shankle et al., 1998; Collins et al., 2010; Cahalane et al., 2012, Charvet et al., 2013; Ribeiro et al., 2013; Workman et al., 2013]. For instance, neurons per unit of cortical surface area vary by a factor of close to two or more between the rostral and caudal pole in cats and monkeys, as is evident in the owl monkey (fig. 2). Species (e.g. carnivores, primates) with increased isocortical neurons tend to exhibit a greater disparity in neurons per 'cortical column' between the rostral and caudal pole [Charvet et al., 2013]. As developmental schedules lengthen, the difference in neurogenesis duration between the rostral and caudal pole increases,

and the disparity between neurons per unit of cortical surface area in adulthood increases. Although there is very little data on developmental duration and isocortical neuron numbers in taxa other than primates, rodents and carnivores, an inclusion of species from other taxonomic groups (e.g. dolphins, elephants) may serve to further test these hypotheses in the future.

The surface area and the volume of the rostral (i.e. frontal cortex) and caudal pole (e.g. primary visual cortex) both expand with positive allometry relative to other cortical regions [Bush and Allman, 2004; Kaskan et al., 2005]. Because neurogenesis duration in the caudal pole is protracted relative to the rostral pole, it is expected that, as overall developmental schedules lengthen, neuron numbers in the caudal regions should increase faster than neurons located towards the rostral or frontal pole. What causes the positive allometry of the frontal cortex? First, since the frontal pole proliferates at an earlier stage of overall cortical maturation, it may have a proportionately longer period of symmetric divisions producing founder 'radial units' [Rakic, 1995]. Second, the cellular organization underlying the disproportionate expansion of rostral and caudal poles should be different. That is, according to our model, the frontal cortex might expand by decreasing neuronal densities and/or increasing the size of neurons, whereas the expansion of the caudal cortex would be accompanied by an increase in neuron numbers. We
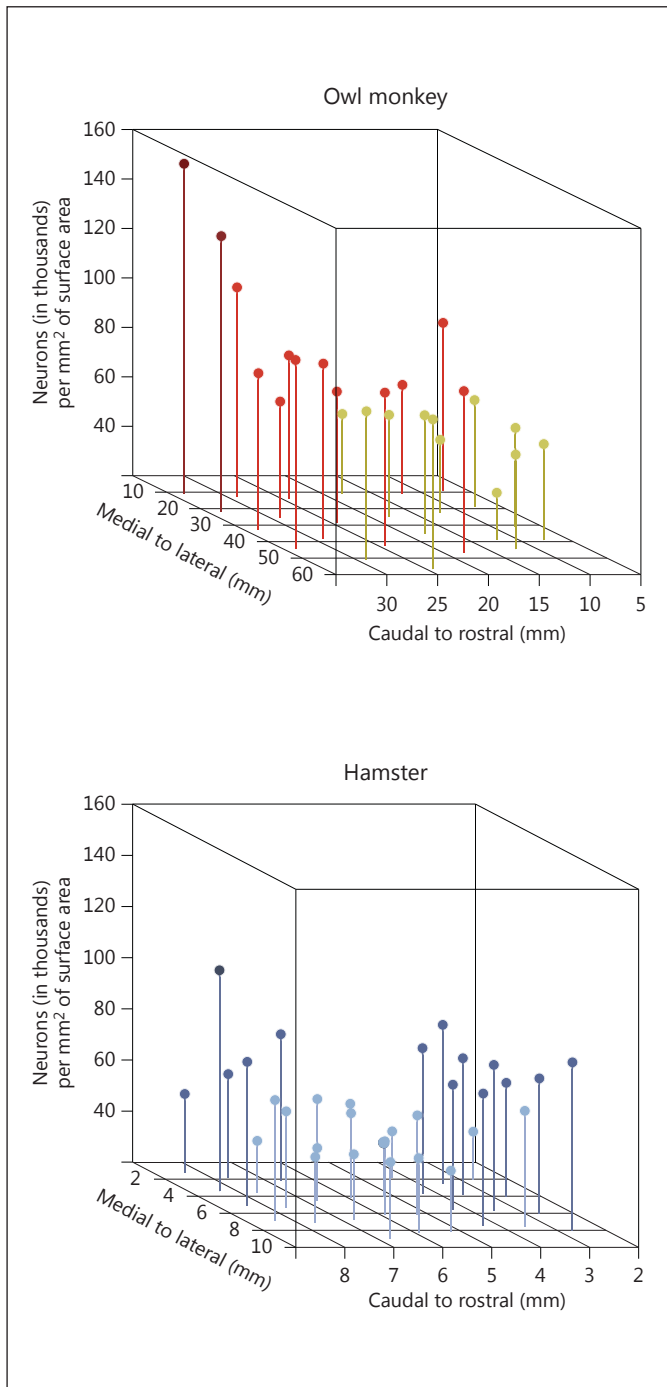
Fig. 2. Neuron numbers per unit of cortical surface area in an owl monkey *(Aotus trivirgatus)* and in a hamster *(Mesocricetus auratus)*. Neuron numbers per unit of cortical surface area increase from the frontal to the parieto-occipital cortex in the owl monkey, but this systematic variation is not clear in the smaller-brained hamster.

next investigate how gradients of developmental schedules may alter the cellular architecture across the rostro-caudal axis of the isocortex and across species.

Influences of Developmental Gradients on Cellular Architecture

Neuronal soma size, dendritic arbors and dendritic spines vary extensively across the isocortex [Jacobs et al., 2001; Elston et al., 2001; Travis et al., 2005; Ballesteros-Yáñez et al., 2006; Benavides-Piccione et al., 2006; Elston et al., 2006; Bianchi et al., 2013]. Most of the variation in dendritic arbors observed across the rostro-caudal axis falls in line with the axes of variation in neurons per unit of cortical surface area. In some brain regions, neurons that are born early are generally larger than neurons that are born later in development [Crossland and Uchwat, 1982; Hickey and Hitchcock, 1984]. Neurons with larger somas typically have larger dendrites than those that have smaller somas [Bok, 1959; Elston et al., 2001; Jacobs et al., 2001; Elston, 2003; Elston et al., 2006; Elston and Manger, 2014]. Larger dendrites imply more dendritic spines and more synapses per neuron. In the isocortex, neurons are generally bigger and exhibit larger dendritic arbors and more dendritic spines in the rostral pole than in the caudal pole. For instance, neuronal soma size in layers II/III varies along a continuum between the rostral and caudal pole in several species of New World monkeys (fig. 3) [Cahalane et al., 2012] with larger cells observed in the rostral pole compared with those observed in the caudal pole. Layer III pyramidal neurons in the rhesus monkey are 16 times more spinous in the rostral pole (i.e. prefrontal cortex) than in the caudal pole (i.e. primary visual cortex). That is, in primates neuronal somas have a tendency to enlarge, have more elaborate dendritic branches and become spinier towards the frontal cortex [Jacobs et al., 1997; Elston et al., 2001; Jacobs et al., 2001; Elston et al., 2005, 2006; Anderson et al., 2009; Elston et al., 2011; Jacobs et al., 2011; Bianchi et al., 2013].

As neurogenesis duration between the rostral and caudal poles of the isocortex increases, the disparity in neuronal soma size also has a tendency to increase in some taxonomic groups. Although developmental schedules have not been fully investigated in New World monkeys, total isocortical neuron numbers may be used as an estimate of developmental timing with the assumption that a lengthened developmental schedule is necessary to produce more neurons. The difference in soma size in layers II/III pyramidal neurons between the rostral and
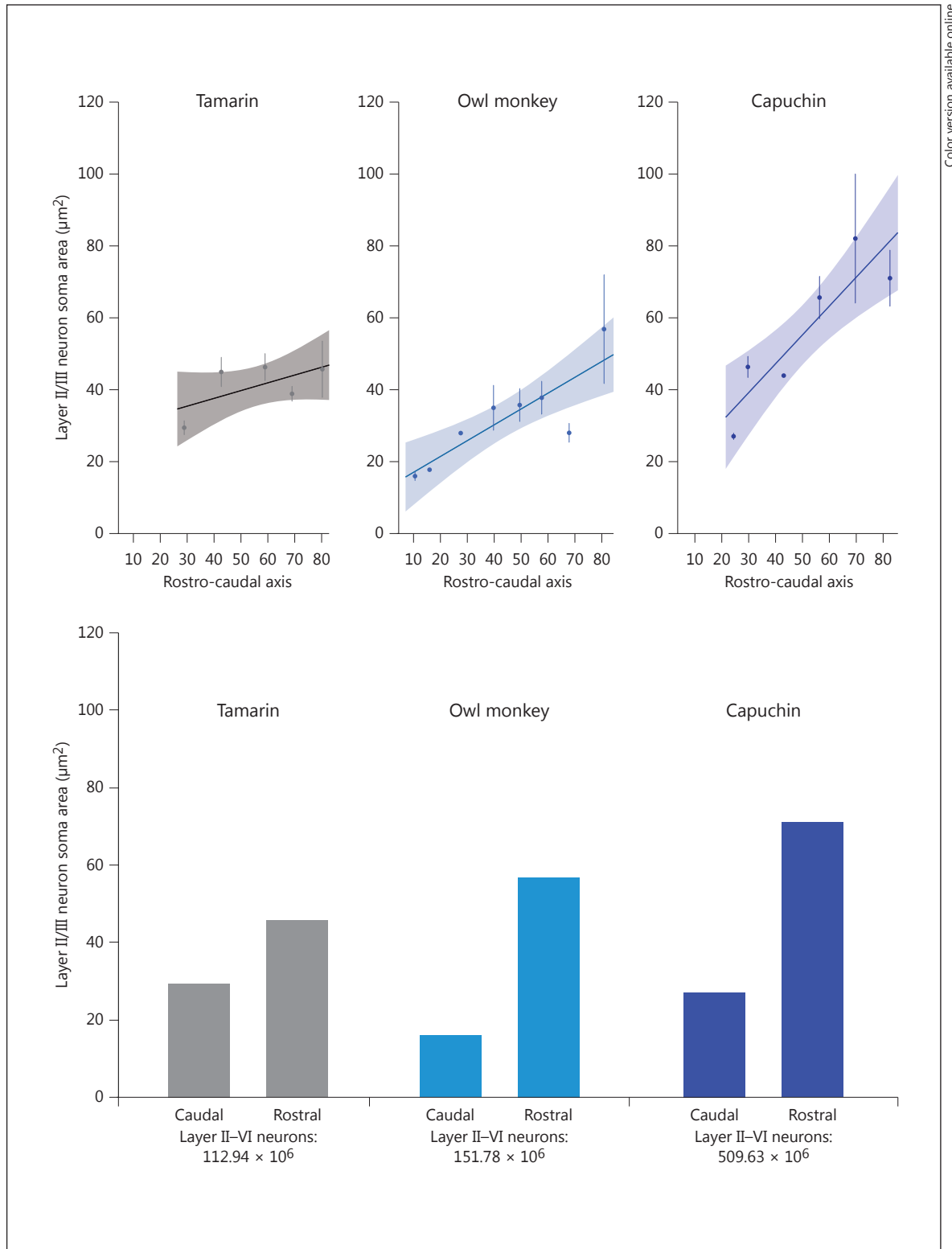
Fig. 3. Layer II/III neuronal soma size plotted against the rostro-caudal axis of the isocortex in three species of New World monkeys. These data show that as overall isocortical neuron numbers increase (i.e. layer II–VI neuron numbers), the discrepancy be- tween layer II/III neuronal soma size between the frontal and pa-rieto-occipital cortex increases in these taxa. These data are from Cahalane et al. [2012] and Charvet et al. [2013].

caudal pole increases as overall isocortical neuron numbers increase in New World monkeys. For instance, isocortical neurons in the capuchin *(Cebus apella)* are four times more numerous compared with the tamarin *(Saguinus midas;* fig. 3) [Charvet et al., 2013]. Soma size varies relatively little across the rostro-caudal axis of the tamarin isocortex, but the difference in soma size varies more than 2-fold between the caudal and rostral pole in the capuchin [Cahalane et al., 2012]. Among apes, the disparity in neuronal soma size across the rostro-caudal axis of the isocortex has a tendency to be larger in humans than in chimpanzees *(Pan troglodytes),* although these differences were not statistically significant [Bianchi et al., 2013]. How soma size varies in accordance with spatiotemporal gradients of neurogenesis across a broader range of species has yet to be investigated [Benavides-Piccione et al., 2006; Jacobs et al., 2010; Bianchi et al., 2011].

Dendritic arbors consistently enlarge towards the frontal cortex within a species. Whether the disparity in dendritic arbor size across the isocortical rostro-caudal axis varies consistently across species is not clear [Bianchi et al., 2011, 2013; Jacobs et al., 2011]. Dendrites of neurons do have a tendency to become progressively spinier in the frontal cortex as developmental schedules lengthen and brains expand [Elston et al., 2001, 2006]. In primates, the total estimated spine numbers in layer III pyramidal neurons vary relatively little across the rostro-caudal axis in the small-brained marmoset brain, more in the macaque and substantially more in humans (fig. 4). Most of this variation is due to species differences in spine density in the frontal cortex rather than variation in the occipital cortex. The variation in dendritic spine numbers may have important implications for how the cortex processes information across its rostro-caudal axis.

Integration across the Isocortex

The difference in neuronal size, including soma and dendritic spines, between the rostral and caudal pole may index the integration of information across the rostro-caudal axis. Within the isocortex, association cortical areas integrate information from primary cortical areas (e.g. primary visual cortex) and are located towards rostral-to-primary cortical areas [Felleman and van Essen, 1991]. The progressive integration and summation of visual information from the primary visual cortex moving forward is very well known: the primary visual cortex has
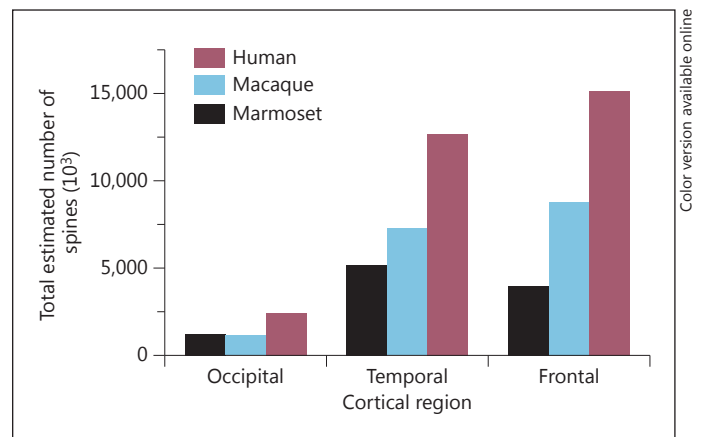

Fig. 4. Estimated total number of spines in layer III pyramidal neurons in prefrontal, temporal and occipital regions in marmosets (8 g), macaques (93.8 g) and a human (1,350 g). The difference in the total number of spines of layer III pyramidal cells between the frontal and occipital cortex is greater in bigger brains. Most of the variation in total estimated spine numbers is in the frontal pole rather than in the occipital region. These data are from Elston et al. [2001].

the smallest receptive fields, greatest temporal resolution, and receptive field size progressively increases with increasing (rostral) distance from the primary visual cortex [Lamme and Roelfsema, 2000]. Similarly, it has been suggested that the frontal cortex gradually processes more abstract information towards the rostral pole [Prabhakaran et al., 2000; Badre and D'Esposito, 2009; O'Reilly, 2010]. The frontal cortex is generally considered responsible for 'executive control' and encodes much longer-term contexts within which these perturbations occur. Developmental gradients across the frontal-to-parieto-occipital axes within these cognitive and sensory domains align with the gradients in anatomical organization. The variation in the cellular architecture across the cortex may 'force' integration of information and reduction of the dimensionality of representations toward the frontal pole, above and beyond the well-described 'feed-back and feed-forward' projection pattern along the same axis.

The emergence of novel methods designed to characterize tracts and patterns of connectivity may provide us with new opportunities to address how connectivity patterns vary across the isocortex and across species. In particular, the use of diffusion imaging may offer new avenues to explore how patterns of connectivity and tracts may vary in accordance with gradients in the timing of the maturation of the isocortex [Lazar, 2010; Takahashi

et al., 2011, 2012; Ingalhalikar et al., 2014]. In the future, we may align the gradients in maturational time, anatomical features, connectivity patterns and cognitive processing across the rostro-caudal axis of the isocortex and across species.

What about Humans?

Humans have a very long developmental timetable compared with all other primates and most other mammalian species [Clancy et al., 2001; Workman et al., 2013]. The difference in duration of neurogenesis between the anterior and posterior pole can be predicted from the general model we have developed for 'translating time' across mammalian species [Finlay and Workman, 2013; Workman et al., 2013]. The difference in terminal neurogenesis between the rostral and caudal pole is predicted to last over an interval of 70 days in humans compared with 29 days in the rhesus monkey (fig. 1). The disparity in neurons per unit of cortical surface area between the anterior and posterior pole should thus be correspondingly greater in humans compared with other primates. This greater disparity in cellular architecture across the fronto-parieto-occipital cortex should emerge not because of selection for this isolated feature but because the constellation of these features is the predictable consequences of humans' very long developmental timetable [Finlay and Workman, 2013].

Although little is known about how neurons per unit of cortical surface and dendritic arbors vary across the isocortex of humans [Jacobs et al., 2001; Anderson et al., 2009], it would be expected that humans should have larger soma sizes in the frontal cortex compared to other primates because of the systematic and inverse relationship of neuron number per column, cell size and dendritic spine number. In line with these predictions, the disparity in neuronal soma size across the rostro-caudal axis of the isocortex has a tendency to be greater in humans than in chimpanzees, although these differences are not statistically significant [Bianchi et al., 2013]. Moreover, humans have higher estimated spine numbers in layer III pyramidal neurons than the rhesus monkey and the marmoset in the frontal cortex (fig. 4). However, one study found that the disparity in the number of spines and dendritic arbors across the rostro-caudal axis of the isocortex is not greater in humans compared with chimpanzees [Bianchi et al., 2013]. Therefore, more data are needed to determine whether humans deviate from the expected allometry.

Many of the observations described above align with the view that many of the observed 'unique' anatomical features within the human frontal cortex are due to allometric variations in the isocortex and are the products of our extended schedule of neurogenesis in the context of 'standard' rules for the specification of cell classes and the establishment of connectivity. Special adaptations, such as changes in connectivity, specific cell classes, speed or specificity of learning mechanisms within the human cortex, in any number of aspects, may certainly exist. We argue that a search for derived characters within the human cortex should focus on departures from the systematic and allometric variation across its axis. This is not to say that humans may not have been selected on those computational features permitted by the progressive change in cortical organization outlined here. The locus of likely genetic change, however, would not be found in a mechanism specifying a 'new' frontal cortical area, or a larger dendritic arbor of certain pyramidal cells, but would rather be observed in a longer period of brain generation and development, in the context of our environmental and cultural niche.

Behavioral Implications

The observation that variation in isocortical anatomy is systematic across primates despite these species filling different niches suggests that the large-scale global changes in the isocortex described here are not directly tied to behavior, ecology or niches. That is, the isocortex employs these developmental changes and its flexible nature may allow the organism to adapt to its environment [Charvet and Finlay, 2012].

The timing of developmental schedules may foster changes in what individuals learn. Longer developmental schedules may entail extended parental care and extend the duration in which individuals learn from conspecifics [Charvet and Striedter, 2011]. Lengthening developmental schedules may foster, but may not be sufficient to modify, what is learned in development. Cetaceans and elephants develop for a long period of time and show impressive behavioral abilities, but they are not conducting seminars on the distinctions of their own brains [observation modified from P. Rakic, in Molnár and Pollen, 2014]. We suggest that 'species-specific' adaptations, other than increased computational capacity, should be sought outside the isocortex, in social and motivational circuitry. What is learnt should depend on what is intrinsically rewarding to attend to, and what information

populates the cortex. Unlike the sparse-to-nonexistent catalogue of genetically linked, adaptive changes in local cortical features, demonstrations of adaptive changes in the circuitries mediating motivational behaviors are many and growing in number [Goodson and Thompson, 2010; Syal and Finlay, 2011]. Species differences in exploratory behaviors during postnatal development may link social attention and learning capacities. For instance, domesticated dogs and wolves differ in their behaviors and attention to human signals shortly after birth [Gácsi et al., 2005; Virányi et al., 2008]. Evolutionary changes in exploratory behaviors and the motivational circuitries underlying them may contribute to important behavioral differences in adulthood [Miklósi et al., 2003; Kaplan and Oudeyer, 2007]. A lengthened developmental schedule that simultaneously provides a powerful cortical matrix for information extraction and an extended learning period, coupled with directed changes in motivational and exploratory circuits, may be all that is necessary and sufficient to account for our unique features.

Acknowledgements

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