

Developmental mechanisms channeling cortical evolution

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Increase in the area and neuron number of the cerebral cortex over evolutionary time systematically changes its computational properties. One of the fundamental developmental mechanisms generating the cortex is a conserved rostrocaudal gradient in duration of neuron production, coupled with distinct asymmetries in the patterns of axon extension and synaptogenesis on the same axis. A small set of conserved sensorimotor areas with well-defined thalamic input anchors the rostrocaudal axis. These core mechanisms organize the cortex into two contrasting topographic zones, while systematically amplifying hierarchical organization on the rostrocaudal axis in larger brains. Recent work has shown that variation in ‘cognitive control’ in multiple species correlates best with absolute brain size, and this may be the behavioral outcome of this progressive organizational change.

Size-dependent scaling of cortical organization

The cerebral cortex is the structure that changes the most in absolute and relative volume across the mammalian lineage [1]. The nature of the transformation the cortex makes to support evolving functions ranging from motor skills to moral reasoning has been the focus of research for decades. Contrasting aspects of cortical organization are emphasized depending upon the theoretical interests of each researcher. By contrast, the differentiated mosaic of cortical cytoarchitectonic areas can be highlighted, emphasizing species-specific specializations. These specializations can include relative volume allocation, modifications in circuitry, and regulation of time and type of environmental instruction, for diverse functions ranging from the palpating organ of the star-nosed mole [2], echolocation in bats [3], to language (e.g., [4,5]) or face recognition [6] in humans. By contrast, the apparent uniformity of cortical columns in selected locations and species [7,8], and the possible uniformity of its computation [9,10]; the extended period often required for mature cortical organization to emerge (e.g., face perception [11]); the orderly representation of learned dimensions of categorization in vision and language [12,13] and the myriad instances of plasticity and functional remapping in normal and abnormal cortical function [14] convince others that the

cortex is best viewed as a generalized computational device. Independently of the merits of either argument, however, both share a hidden assumption that the changing functionality of the cortex takes place within a device whose organization is the same at multiple scales. Little consideration has been given to the possibility of systematic change in the organization of the entire cortex at different sizes.

The cerebral cortex ranges in size to an astonishing degree, considering only the terrestrial range – from the smallest shrew to the largest elephant – represents a size range of 5–6 orders of magnitude [1], and it is reasonable to raise the question of whether the cortical sheet itself remains stable in its properties over this range. A different approach, ‘evo-devo’, proves useful to this end. The subjects of evo-devo research are the multiple interactions of developmental mechanisms and evolution; for example, the stabilization of ‘evolvable’ developmental mechanisms robust to scaling and common perturbations [15], and the constraints imposed by pleiotropy in the employment of genes or developmental mechanisms [16], niche construction, and cultural evolution [17]. Although evo-devo research has recently become associated predominantly with the genomics of early body-plan organization, those who initially developed the term had a much broader view of its range and the phenomena to which it might apply [15,18]. We reclaim here the evo-devo approach for brain and behavior to look at how the developmental mechanisms that organize the cortex are implemented at different scales. We will argue that the cortex is transformed in a particular manner over its range in absolute size, and that this is the systematic result of the properties of the conserved mechanisms that generate it. This transformation seems likely to be an immediate source of computational and behavioral changes associated with increased brain size, reflected in an increasing hierarchical structure of analysis important in sensory integration, predictive coding, and cognitive control.

A basic organizational scheme for the cortex

We present a scheme that highlights features of the cortex relevant to fundamental developmental mechanisms, some of which are stable and some variable in cortices of varying size (Figures 1 and 2; Box 1). We adapt our base representation from the recent multilab, extensive neuro-anatomical mapping and analyses of connectivity of the entire macaque lateral and limbic cortex [19–24]. These studies are a systematic updating and extension of the original ‘Van Essen diagram’ of the connectivity of

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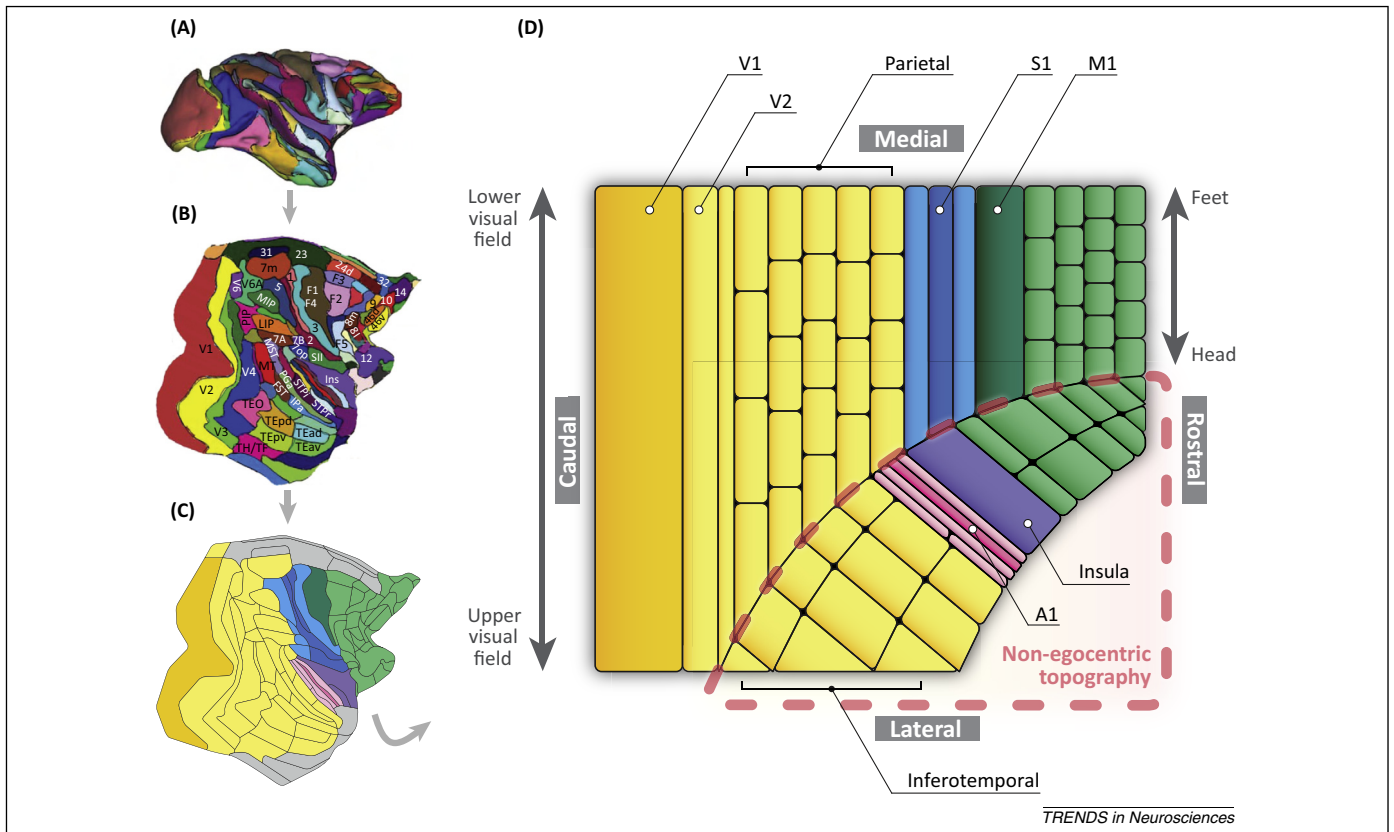


Figure 1. Procedure for schematizing the cortical sheet. (A) Lateral view of a 3D-reconstructed right cortical hemisphere of an individual macaque (*Macaca fascicularis*). (B) A flattened representation of (A). (C) The map in (B) divided into compartments of internal topographic continuity [53,54], each associated with a unique primary sensory or motor area. (D) Further schematization of (C), now excluding limbic cortex, with emphasis placed on longitudinal stripes of cortical areas extending along the mediolateral axis of the unrolled cortex. The cortical sheet is segregated into two zones with differing topographic organization, one egocentric and the other non-egocentric. (A) and (B) are reproduced, with permission, from [21].

macaque posterior cortex [25] (Figure 1). First, the right isocortex of an individual macaque monkey (Figure 1A) is flattened and unrolled, with two cuts on the medial aspect of the cortex, up to the frontal pole, and up to the occipital pole; these procedures were chosen to minimize areal distortion (Figure 1B). For the representation employed in this paper, first, cortical zones are grouped into visual, auditory, somatosensory and motor regions, emphasizing evolutionarily-conserved primary sensory and motor areas (Figure 1C). The final schematic (Figure 1D, Box 1) regularizes and orients cortical areas on the relevant rostrocaudal and mediolateral axes to highlight the mediolateral ‘stripes’ that cut across sensory and motor domains. In the text relating to these representations, we use only the terms ‘number of neurons per mm²’ or ‘unit surface area’ to avoid the multiple developmental, evolutionary [26], morphological, and functional associations that have accrued to the term ‘cortical column’ [27,28].

Developmental organizers of the cortex

A rostral-to-caudal gradient in the duration of neurogenesis (Figure 2A)

A large and systematic inhomogeneity in the number of neurons per mm² of cortical surface across the cortical sheet escaped notice for a very long time, and the claim was made that the number of neurons under a unit area of cortical surface was uniform, excepting primary visual cortex [7,8]. Contests to this assertion focused on area-by-area

mosaicism [29–31], rather than systematic cross-area gradients or cross-species differences. The persistence of the view of cortical uniformity arose from several experimental and natural sources. The rostral and caudal poles of the cortex, where numerical discrepancies are the greatest, were systematically avoided by researchers attempting to avoid biases caused by sections not normal to the cortical surfaces, where the cortex curves around at its poles. The best-studied brains, those of rodents, are in fact more uniform across their surfaces. Interestingly, whether related to some unknown aspect of function or a coincidence, the decrease in neuron numbers per unit surface area in rostral cortex is balanced by an increase in volume of connectivity, such that the depth of cortex is roughly similar throughout the extent of the cortex, even in the largest brains. Perhaps most important, the stable cellular components of the cortex in every size of brain assert a basic uniformity even in the face of regional and species differences.

Using flow cytometry of homogenized cortices in a set of primate brains, a gradient of neuron number per unit of cortical surface area increasing from front to back was observed [32] (Figure 2A). Further statistical analyses of these data revealed a relationship of the gradient to brain size, as well as a ‘bump’ in primary sensory areas in neuron number [33]. This method, however, does not study the allocation to layers.

Note that we are describing a principal axis of variability in cortical neuron number aligned at origin with a

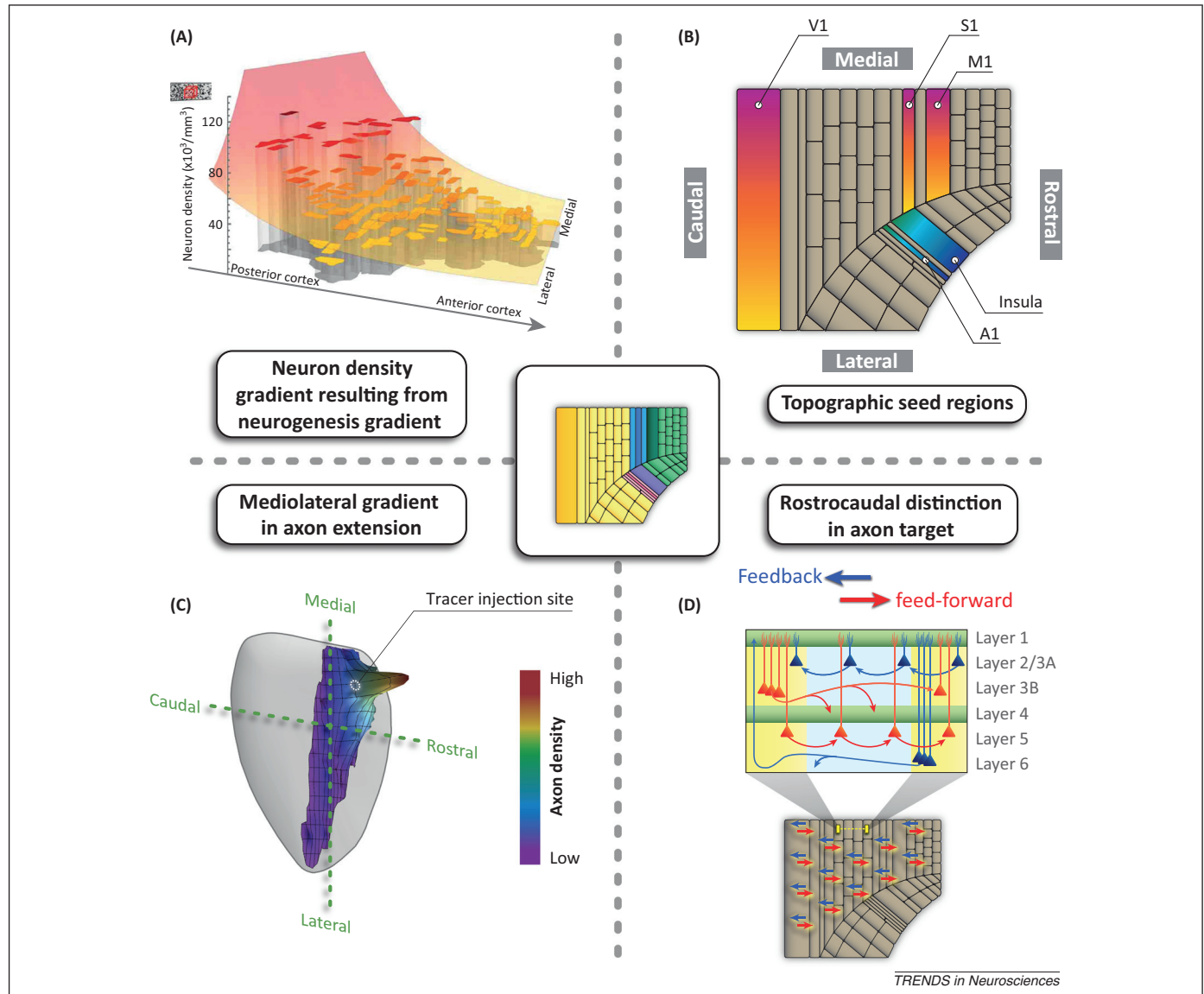


Figure 2. Four developmental mechanisms that organize cortical architecture along the rostrocaudal axis. **(A)** The rostrocaudal gradient of neuron number per unit surface area found in adult brains is a consequence of differential duration of neurogenesis along the rostrocaudal axis in the early developing brain. Reproduced with permission, from [30]. **(B)** The positions of sensory and motor ‘seed regions’ within the cortical schematic, showing primary visual, somatosensory, and motor cortex in red-orange within the dorsal egocentric topographic region, and primary auditory cortex and the insula in blue-green within the non-egocentric map. **(C)** An example of the distribution of initial axonal arborizations from a single cortical injection site in a neonatal hamster cortex. The cortex is unrolled and flattened, and the number of axon crossings at each location is represented both by height from the cortical surface and color temperature. The injection site is at the peak of axon density. Early axon extension was maximal on the mediolateral axis and restricted on the rostrocaudal axis. Adapted, with permission, from [30]. **(D)** Schematic of the pattern of feed-forward and feedback projections along the rostrocaudal axis. The schematic of these projections in a cortical section is abridged and redrawn, with permission, from [24].

developmental rostrocaudal axis, and are not claiming that this axis is the sole source of variation in neuron number per unit cortical surface area. Using sectioned material in which neuron type and lamina could be identified, with stereological corrections, Charvet and colleagues showed, in a further three New World monkeys and three rodents (Figure 3A), that the cross-cortex gradient was produced entirely by the upper cortical layers (2, 3, and 4) with the slopes of the gradient positively correlated with brain size [34], corresponding well to extrapolations from the previously studied primate brains [33]. In the largest brains, such as that of the baboon, the ratio of number of neurons under a mm² of cortical surface area, comparing caudal to rostral, is about 3 to 1; in rodents, about 1.2 to 1; and in smaller monkeys the ratio is intermediate. Of course, further differences in local neuron density, number, and

type by layer co-occur with this cross-cortex gradient. Considering cortical areas, for one example of many, the ‘granular’ versus ‘agranular’ description of cortical areas is a further important distinction to be made. Considering diverse examples from taxonomic groups, cortical thickness and gyrification patterns vary systematically between mammalian taxonomic groups [35]; rodents have relatively more glial cells per neuron in the cortex overall [36], and neuron condensations often reflect species-typical sensorimotor specializations, the prototypical case being the ‘barrel fields’ of rodents [37]. The cortex of each species and every cortical area is the result of multiple differentiating forces, some local, and some general.

The source of the rostrocaudal difference in neuron number in the mature cortex of various species is almost certainly the difference in the rostral-to-caudal duration of

Box 1. Two zones of contrasting topology in the cortex

The cut and flattened macaque cortex representation of Markov and colleagues [21], further schematized in this paper (see Figure 1 in main text), brings out some features of the cortex that are difficult to appreciate in the normally folded and molded cortex. One emerging organizational feature is that two large regions of contrasting topologies separate themselves within the cortical sheet (see Figure 1D in main text). A rough dorsolateral wedge, delimited by primary visual cortex, the medial boundary of parietal cortex with limbic cortex, the frontal pole, and the most lateral points of (unrolled) primary motor and somatosensory cortex, has a multimodal, egocentric topography. Along the medial boundary, the lower visual field and sensation and movement in the lower extremities are represented, and, along the lateral diagonal, the upper visual field and sensation and motion of the head and arms are located. Within this egocentrically organized wedge, all degrees of spatial topographic 'acuity' within the visual and somatomotor regions can be seen, from the point-to-point representations of primary visual and somatosensory regions, to the minimal 'reaching' topography of external space in parietal cortex [84]. Within the visual system, this zone can be recognized as the area designated for 'spatial vision' [85], the 'dorsal stream' [25], or Goodale's 'how' or 'action' pathway [86].

By contrast, the temporal region is characterized by topologies that, although they might represent space with precision as an aspect of other dimensions of representation, do not represent it in an egocentric frame. Within vision, these representations may be classed as 'perception', the 'ventral stream', or the 'what' pathway as above [24,85,86], and much current work has aimed to describe such things as the layout of the elements of scenes, 'contexts', objects, and body parts (e.g., [12,87]). It is interesting to realize that the tonotopic representation of the cochlea also finds its place in the nonegocentric zone, adjoining the insula, which represents the similarly non-egocentric gustatory, general chemosensory, and other viscerosceptive representations.

neurogenesis that has been observed in every mammal studied to date [38–41]. In general, the first generated neurons can be found over the entire cortex at once, but cessation of neurogenesis is graded, being later at the caudal pole, and ranging from differences of less than 1 day between rostral and caudal regions in mice to around 3 weeks of extended generation in monkeys. These gradations in duration are well fit by our multiple-species 'translating time' models [42,43]. Using the basic formal structure developed by Caviness, Nowakowski, Takahashi, and colleagues for examination of cortical neuron production and control of cell cycle in mice [44,45], we have developed a further model which produces the changing cortical area, number of neurons per unit surface area, and changing laminar distribution of neurons from specified founder populations for a large range of species [46].

In summary, when the cortex grows in neuron number, in the rodent, carnivore, and primate taxonomic groups investigated so far, it not only increases in surface area and number of cortical areas but also preserves the same number of neurons under a unit cortical surface area everywhere. In small brains, the number of neurons per cortical mm² of surface area is relatively uniform, and the principal difference we observed was the disposition of neurons between supragranular and infragranular layers. In larger brains, the number of neurons per unit surface area also becomes larger, and the variation in this feature becomes increasingly larger, greatest toward the occipital pole. The granular and supragranular layers, 2–4, are the source of this nonuniformity. The relative duration of

neurogenesis coupled with measured cell cycle control parameters can easily produce these changing distributions [46]. Recent examinations of gene expression across the cortical surface show a corresponding pronounced rostro-caudal gradient produced by multiple gene classes, raising new prospects for mechanistic investigation [47,48].

Topographically organized 'seed' regions (Figure 2B)

Across all the mammalian radiations, only a small number of cortical areas are unambiguously homologous in the larger brains of large taxonomic groups (e.g., rodents, carnivores, or primates) and present in all members of those groups [49,50]. These are the primary sensory regions, visual, somatosensory and auditory, and the primary motor cortex. These areas are recognized by the primary thalamic projection they receive, the topographic representation of the sensory surface they contain, and their rostral-to-caudal order – which is somatomotor, auditory, then visual (Figure 2B). Each identifiable region, that is, each primary area, and each interposed parietal, temporal, and frontal region generally has its own characteristic allometry (relative rate of volume increase with respect to the whole cortex), with parietal and frontal regions showing the most positive allometry [51]. Whether particular regions are allometrically 'unexpected' in particular species, particularly frontal cortex in humans, is a matter of continuing debate (e.g., [52,53]). In an earlier study of the number of cortical areas in a variety of mammals including marsupials, shrews, carnivores, and primates, drawn from studies where cortical areas were defined in a consistent manner [54], the total number of recognized 'areas' increases fairly linearly with total cortex area up to an intermediate brain size, and then more slowly, raising the possibility that two mechanisms are at play. The topographic maps by which we recognize areas may self-organize from initially diffuse projections until some scale beyond which the necessary cellular interactions for self-organization fail.

The primary sensory areas are developmentally privileged in multiple respects. In the initial polarization of the cortical sheet [55], their differential gene expression and early innervation make them the only recognizable landmarks whose position can define cortical polarity. The thalamic nuclei that innervate primary sensory areas are generated earliest and innervate them first [43]. Thalamocortical axons appear to instantly and accurately 'recognize' the route to and terminus of their cortical target region [56], and form topographically correct maps at once, subject to later, experience-dependent modifications [57,58]. The mutual recognition and trophic dependence of corresponding thalamic nuclei and cortical areas is such that it is impossible to 'miswire' them in the sense of inducing new thalamic inputs of any substantial number into an area, although existing projections may adjust their relative volumes [59]. Successful rewiring attempts have employed rearrangements of input to the thalamus, not the cortex, for such analyses [60].

Interesting and undeservedly neglected initial studies of the organization of thalamocortical projections in rodents by Caviness and Frost found corresponding 'compartments' in both thalamus and cortex, as indicated in

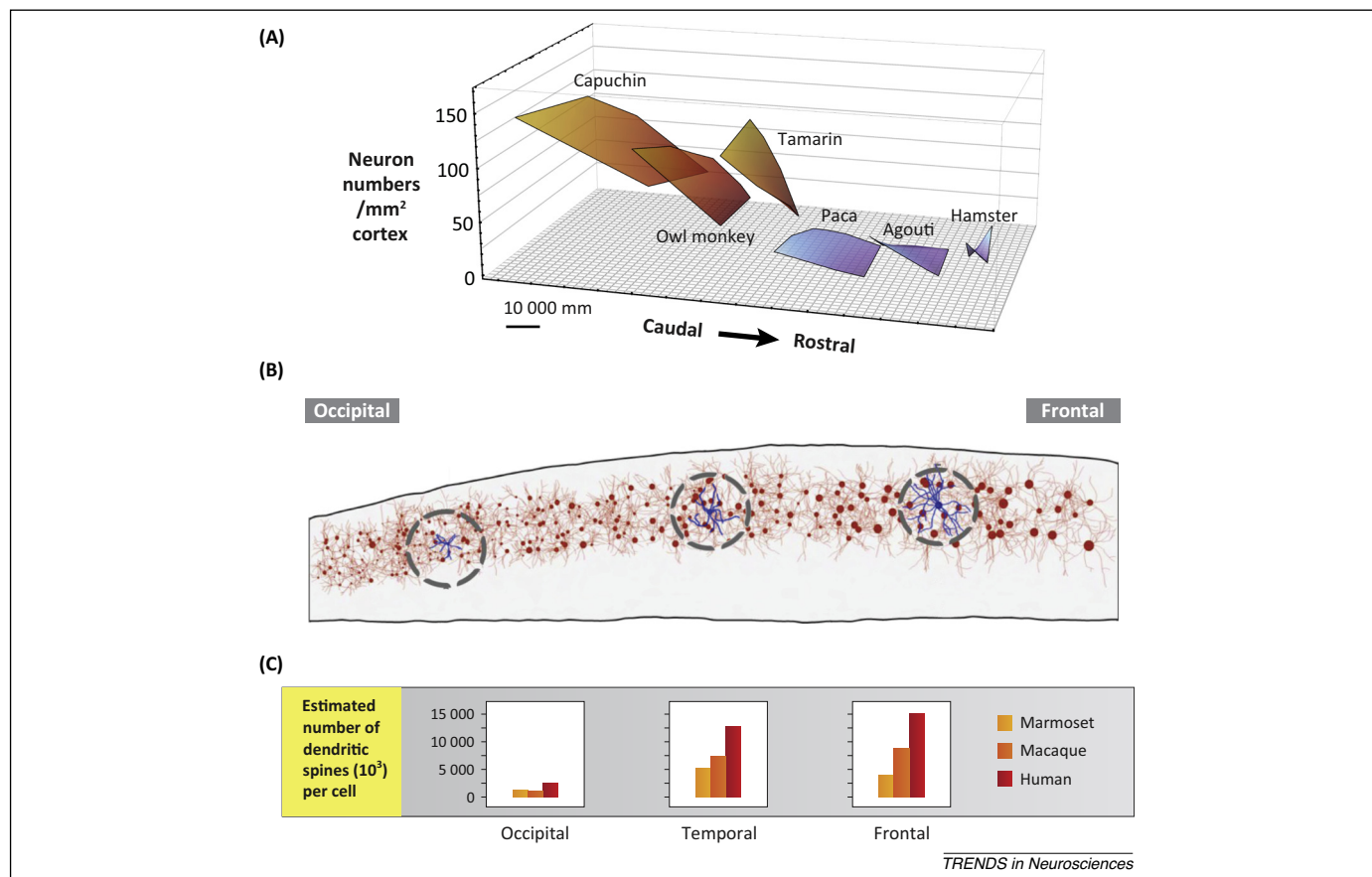


Figure 3. Structural and morphological changes along the rostrocaudal axis that are amplified with increasing brain size across species for the cortex overall, and for single neurons. **(A)** Representation of the surface area of the cortex for three primates and three rodents arranged in order of decreasing cortex size. The extended cortical area of each species is oriented caudal to rostral. The z-axis represents total neuron numbers per mm² of cortical area at each point in every cortex, thus representing neuron numbers within and between species by the relative height and tilt of each sheet. Adapted, with permission, from [31]. **(B)** A schematic of the cellular correlates of neuron number per unit surface area disparities along the rostrocaudal axis in an idealized saggital section. The distribution of increases in soma size, a decrease in neuronal density, and increase in dendritic arborization are estimated to fit the disparity in neuron numbers on the rostrocaudal axis for the baboon illustrated in Figure 2A. Adapted with permission from [30]. **(C)** Relative number of dendritic spines in layer 3 pyramidal neurons in prefrontal, temporal, and occipital regions in marmosets, macaques, and a human. Brain masses for each species are 8 g, 93.8 g, and 1350 g, respectively. Spine numbers systematically reflect both cortical position, and overall cortex size. Adapted, with permission, from [62].

Figure 2B [61,62]. Within these compartments, the nearest-neighbor relationships of the sensory surface represented are maintained across thalamic nuclei and cortical area boundaries, producing, for example, the center-to-periphery, periphery-to-center, and center-to-periphery mirror reflections of the visual field when progressing from V1 to V2 and V3 [25]. These observations suggest the interesting possibility that these regions self-organize later in development than the seed regions, a possibility under current investigation. Such a conjecture has recently been explored for the formation of the V1–V2 boundary [63].

Anisotropic spread of initial intracortical axonal arbors along the mediolateral axis (Figure 2C)

A recent examination of the overall organization of intracortical fiber pathways in several species of macaques [64] demonstrated a strong orthogonal arrangement of fiber pathways. That is, ‘cortico-cortical pathways formed parallel sheets of interwoven paths in the longitudinal and medio-lateral axes, in which major pathways were local condensations’. Although there are multiple studies of the establishment of intracortical connections, emerging from specific sites (e.g., [65]; reviewed in [66]), there are very few

studies of the overall emergence and early structure of intracortical connectivity across the entire cortical sheet. Our laboratory undertook an investigation of the first emergence of intracortical connectivity, analyzed over a grid of injection sites in the rodent cortex [67]. A major result of this analysis was the demonstration of a strong anisotropy of earliest projections, extending and arborizing preferentially along the mediolateral axis but restricted on the rostrocaudal axis (sample reconstruction of one injection result, Figure 2C). When the network structure implied by this pattern of outgrowth was compared to more symmetric outgrowth networks, several useful features emerged, including ‘saving wire’ and early promotion of hub structure [67]. A replication and extension of this work in other species, particularly in those with larger cortices, would be highly informative. Minimally, this pattern of distribution would seem to prioritize within-area organization, such as that described for the elaboration of connectivity between orientation columns [68].

‘Feed-forward’ and ‘feedback’ connections along the rostrocaudal axis (Figure 2D)

A long-known central organizing feature of the cortex, particularly between visual cortical areas, is the fact that

axons projecting rostrally ('feed-forward' connections) project primarily to layer 4, while 'feedback' projections project outside of layer 4 [24]. This feature has been used to establish 'distance rules' between cortical areas to construct models of cortical organization [25,69]. Given the previously discussed relationship of relative numbers of supragranular neurons under a mm^2 of cortical surface to overall cortex size, it is interesting that it is the relative strength, distance and degree of diffuse spread of projections from supra- and infragranular neurons that establish the differences between feed-forward and feedback projections (Figure 2D) [24]. During development, the emergence of feed-forward projections precedes and appears to guide the organization of feedback projections [70]. The application of the preceding definition of feed-forward and feedback becomes complex in regions of agranular cortex, or in areas where diverse modalities adjoin each other, as in inferotemporal cortex, and awaits further anatomical analysis [22].

Summary of developmental features reflected in cortex evolution

The study of the evolution together with the development of the cortex gives two different snapshots of the brain in motion, pointing at features of organization whose importance might be missed if looking only at the static organization of a particular species at maturity. In this case, every conserved feature of cortical development points to the central organizing role of its rostrocaudal axis. As the cortex enlarges in area, the disparity in number of neurons under a unit surface area along the rostral-to-caudal axis increases in parallel (Figure 2A). Incoming sensory information is entered with extreme specificity at fixed points along this axis, to contact equally specific motor output in the frontal cortex (Figure 2B). Initial intracortical axonal connectivity respects this same axis in several ways, preferentially extending orthogonally to it to first establish intra-areal connectivity (Figure 2C). For growth on the rostrocaudal axis, connections going rostrally are different in kind from those extending caudally (Figure 2D). Thus, an enlarging cortex cannot be described simply as a growing network of associatively connected modules. Information appears to be gathered either dorsolaterally into an egocentric topographic mapping, or into a non-egocentric topographic region, including inferotemporal cortex, the primary and secondary auditory cortices, and the insula (Figure 1D, Box 1). Axonal projections have a strong directional component along the rostrocaudal axis, which together with the progressive reduction of neuron number per mm^2 of cortical surface area and the volume of cortical areas, must force a strong compression of representations, or reduction of dimensionality as they are fed along the caudal-to-rostral axis.

Structural and functional consequences of evolutionary differentiation of the rostrocaudal axis of the cortex

Organizational features at the level of the neuron

Figure 3A shows a representation of the neuron number per unit surface area across the cortical surface for six species, three rodents and three primates, arranged from left to right in order of decreasing brain size, sharing the

same z -axis [34]. Figure 3B shows a schematic of the consequences of the neuron-number gradient for the size, density, and arborization of single neurons, in a single 'sagittal' section. This schematic estimates these cell parameters to correspond to the scale of the baboon neuron-density gradient shown in Figure 1A. In primates, the disparity in neuronal soma size from rostral to caudal varies with cortex total area, with the largest disparities being between the supragranular layers of the largest brains [71]. Dendritic arbor volume varies similarly on the same axis [72,73]. In addition, the number of spines per layer 3 pyramidal cell varies with both brain size and cortical position (Figure 3C) [71,74]. Comparing species, it is the relative increase in the size, and arbor and spine number of frontal neurons in species with larger brains, rather than a decrease in those values in occipital neurons that distinguishes them.

These changes in neuronal morphology strongly imply an increased input of some kind in frontal neurons, but do not specify its source – which could be immediately local, specific to a region or a functional system, or trans-cortical. There is evidence for the latter two. Within the visual system, receptive field sizes progressively increase with 'distance' from primary visual cortex [75]. Transcortically, the work of Markov *et al.* [24] shows that, in the macaque cortex, approximately twice as many separate cortical areas project to prefrontal cortex than to the occipital visual areas, with parietal and temporal areas in between. Corresponding to this observation, more nodes corresponding to 'rich clubs' of high network connectivity are found in frontal cortex than in other regions [76].

Behavior and cognition

Understanding of the precise virtue of increased brain size for behavioral and cognitive abilities has been elusive. For mosaic views of brain evolution, a longer list of specific competencies should correlate with increasing brain size, but no such analysis has been undertaken, to our knowledge. Across species, greater relative brain size is associated with the general features of more instances of tool-making and innovation, greater success in territorial invasion, and longer lifespan, all of which correlate with each other [77]. Considering normal individual variability in humans, in which differences from the smallest to largest brains echo the allometric patterns of phylogenetic variability with surprising fidelity [78], the relative size of the cortex, particularly in the parietal and frontal regions, correlates with various aspects of intelligence [79]. All these observations, although interesting in themselves, leave us far from a mechanistic account of the relevance of brain size to behavioral capacities, and several outstanding questions remain (Box 2). Two recent observations, however, suggest a more specific link between comparative differences in cognition and the progressively greater differentiation of the rostral-to-caudal axis of the cortex in large brains. In a massive study of some 36 species conducted in multiple laboratories [80], superior performance on two measures of 'cognitive control' was correlated with absolute brain size. In another study of primates alone, the time an individual would wait for a preferred reward was also correlated with absolute brain size [81]. Within the

Box 2. Outstanding questions

- What feature of developmental timing or neural cell biology permits or produces the dramatic difference in convergence on single pyramidal neurons along the rostrocaudal axis of the cortex?
- The limbic cortex was specifically eliminated from the present discussion because it does not show the distinct rostral-to-caudal gradient in neurogenesis of the rest of the cortex. What significance does this have for its integration into overall cortical circuitry?
- The studies cited on cross-species 'cognitive control' included birds as well as mammals, but, of course, birds do not possess a cortex with the organizational properties described here. Can a homolog of a hierarchically organized control system be found in the bird brain?
- When new egocentric topographic maps are introduced into the general two-system structure described in [Box 1](#), such as echolocation in bats, where do they take their place?

frontal lobe, an increasing hierarchy of decision abstraction with progressively frontal position has been described [82]. The increasing convergence of hierarchically arranged multiple cortical areas on a frontal lobe, itself hierarchical [83], may be the direct physical correlate of the ability to compare and decide between behavioral alternatives. The automatic increase in the power of hierarchical organization in larger brains for cognitive control, useful to specialist and generalist alike, and driven by conserved developmental mechanisms, may be the key to understanding the advantage of larger brains in nature.

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