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 neuroanatomical 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
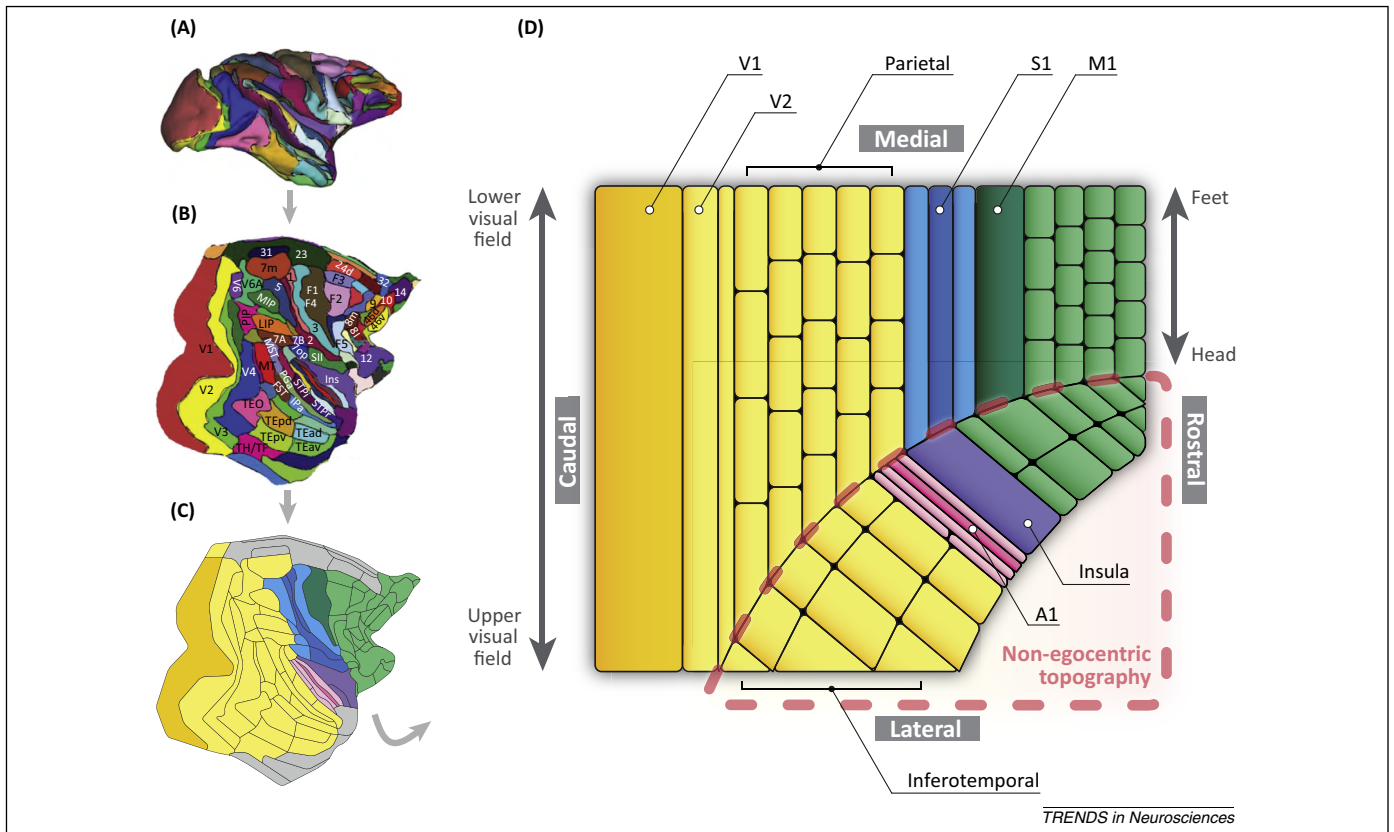
Figure 1. Procedure for schematizing the cortical sheet. **(A)** Lateral view of a 3D-reconstructed right cortical hemisphere of an individual macaque (*Macaca fascicularis*). **(B)** A flattened representation of (A). **(C)** The map in (B) divided into compartments of internal topographic continuity [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 rostro-caudal 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 mm^2' 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 mm^2 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