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Developmental mechanics of the primate cerebral cortex

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Abstract The idea that the brain is shaped through the interplay of predetermined ontogenetic factors and mechanisms of self-organization has a long tradition in biology, going back to the late-nineteenth century. Here we illustrate the substantial impact of mechanical forces on the development, morphology, and functioning of the primate cerebral cortex. Based on the analysis of quantitative structural data for prefrontal cortices of the adult rhesus monkey, we demonstrate that (1) the characteristic shape of cortical convolutions can be explained by the global minimization of axonal tension in corticocortical projections; (2) mechanical forces resulting from cortical folding have a significant impact on the relative and absolute thickness of cortical layers in gyri and sulci; (3) folding forces may affect the cellular migration during cortical development, resulting in a significantly larger number of neurons in gyral compared to non-gyral regions; and (4) mechanically induced variations of morphology at the cellular level may result in different modes of neuronal functioning in gyri and sulci. These results underscore the significant contribution of mechanical forces during the self-organization of the primate cerebral cortex. Taking such

factors into account within a framework of developmental mechanics can lead to a better understanding of how genetic specification, the layout of connections, brain shape as well as brain function are linked in normal and pathologically transformed brains.

Keywords Cerebral convolutions · Axonal tension · Arcuate fasciculus · Laminar thickness · Cortical development

Developmental mechanics

The contribution of mechanical factors to the formation of the cerebral cortical landscape was recognized in classic studies. In the late-nineteenth century Wilhelm His investigated principles of brain morphology with the help of deformed rubber tubes, and explained the cerebral shape by unequal growth, competing volume demands, and resulting tension of different brain structures (His 1874). The work of His and fellow embryologists inaugurated the subject of ‘developmental mechanics’ (Entwicklungsmechanik), which emphasized a causal sequence of developmental events steered by physical forces. In recent decades, such concepts were sidelined by the rapid progress of research into the genetic control of brain development. It may, however, be worthwhile to take a second look at developmental mechanics to understand how the intricate complexity of brain shape and function can arise from a finite number of genes controlling neural development.

The term ‘developmental mechanics’ can be interpreted in different ways. First, it may indicate the contribution of mechanical factors to biological development. Second, and perhaps somewhat closer to its original and more general interpretation, it can be taken as a concept for identifying an orderly sequence of physical, chemical, and physiological mechanisms that provide a causal explanation of development (His 1874).

Naturally, the development of the brain is constrained at each point in time by the laws of physics,

Experiments involving animals were conducted according to the NIH guide for the Care and Use of Laboratory animals (NIH pub. 86–23, revised 1996), and experimental protocols were approved by the IACUC at Boston University School of Medicine., Harvard Medical School., and New England Primate Research Center

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specifically by mechanical forces and physical properties of the biological material. This may sound self-evident, because it is clear that the brain is a physical body and subject to a variety of physical forces. However, physical aspects of brain development have perhaps become clouded by the tremendous success and increasing explanatory power of genetic approaches during the last decades. The challenge, therefore, is to demonstrate the interplay of genetic specification and mechanical constraints during the shaping of the brain.

In the following sections, we demonstrate the contribution of mechanical factors to different aspects of cerebral cortical morphology, such as the relative and absolute thickness of convolutions and the trajectories of cortical projections. In addition, we outline causal mechanisms of cortical development and self-organization that shape the cerebral landscape and influence cellular neural morphology and function.

Formation of cortical convolutions

Several hypotheses have been put forward to explain the existence and shape of cortical convolutions. General aspects of cortical folding, such as the degree of folding, measured by gyrification or isomorphy indices (Zilles et al. 1988; Mayhew et al. 1996), or the average ‘wavelength’ of the convolutions (Richman et al. 1975) can be explained through the buckling of bonded layers of unequal cellular density (Richman et al. 1975), or other mechanical interactions of brain structures, such as friction of the cortical sheet with underlying subcortical structures (His 1874) or the association of the cortical plate with the sub-plate during development (Armstrong et al. 1995). However, these general factors do not explain the specific placement, orientation, and characteristic shape of convolutions. Thus, it has been suggested that convolutions could be formed individually by tailored growth processes (Welker 1990; Armstrong et al. 1995). Another hypothesis holds that the formation of convolutions may depend on the specific organization of long-range projections (Goldman-Rakic and Rakic 1984; Van Essen 1997). The latter hypothesis is particularly attractive, because the characteristic cortical morphology would arise automatically as cortical areas are connected, without the need for individual specification of convolutions. Moreover, a spatial arrangement of cortical regions through the minimization of the axonal tension of interlinking fibers would lead to a reduction of cortical wire and volume (Van Essen 1997). Since the exact development, spatial layout, and density of long-range projections in the primate brain are still not well delineated, it is currently impossible to relate the organization of connections to the specific shape of the whole brain in an analytical way. It is, however, already feasible to explore this relationship at the anecdotal level (Van Essen 1997), and some implications of the mechanical tension hypothesis can also be tested quantitatively. For instance, if the

characteristic shape of cortical convolutions results from global minimization of axonal viscoelastic tension (Van Essen 1997), most axonal trajectories in the adult cortex should be straight, particularly when dense.

In order to test this hypothesis, we determined trajectories and relative densities of prefrontal cortical projections in rhesus monkeys (both sexes). Our connection data included all projection sites and labeled neurons in prefrontal cortices, obtained from a large number of cases with retrograde tracer injections (horse radish peroxidase–wheat germ agglutinin conjugate HRP–WGA; diamidino yellow; or fast blue) in lateral, orbitofrontal, or medial prefrontal cortices (23 cases resulting in 289 projection sites with a total 123,866 projection neurons). Each brain was sectioned serially into 40 or 50 μm in the coronal plane, and all labeled neurons beyond the halo of the injection site were mapped quantitatively in one in every 20 sections. Absolute projection densities were normalized within cases, to provide a measure for the relative density of projections in each case. The trajectories of all projections were also classified as straight (following the shortest path in 3D), intermediate (being slightly deflected), or curved (bending completely around a sulcus). The course of the trajectories was derived from the original serial coronal brain sections, based on the assumption that fibers take the shortest possible path within the white matter from their origin (projection site) to destination (injection site).

Only a few axons (14% of the total in all cases) had curved trajectories, representing mostly sparse projections. By contrast, straight projections were significantly denser, and there was a significant increase of individual projection densities from curved to intermediate to straight trajectories. Moreover, for all prefrontal areas we computed the cumulative (summed) density of projections within each of the three trajectory classes. On average, the combined density of straight projections originating from an area significantly outweighed the density of intermediate or curved projections, even though some individual dense projections followed curved paths (Hilgetag and Barbas 2002). This is consistent with the concept that the shape of the cortical landscape is determined through a global competition of axonal tension forces (Van Essen 1997).

Relative and absolute laminar thickness

It is widely recognized that gyral convolutions of the cerebral cortex are thicker than sulcal ones, (e.g., Welker 1990). Moreover, it has been suggested that forces resulting from the folding of the cortical sheet have an antagonistic impact on the relative thickness of superficial and deep cortical layers (Bok 1959; Van Essen 1997). We investigated if a mechanical impact on laminar cortical thickness could also be demonstrated analytically, using an extensive compilation of quantitative data about the absolute and relative laminar thickness

and cellular density of prefrontal areas in the rhesus monkey cortex (Dombrowski et al. 2001).

Unbiased sampling procedures were employed to estimate laminar thickness, and stereologic procedures were used to estimate the density of neurons by layer using the optical disector (Gundersen et al. 1988). Normative structural data were obtained from five to seven individual cases for each measure. Each brain was sectioned in the coronal plane (40 μm) and stained for Nissl. Measurements from each area and layer were obtained from a minimum of three coronal sections by layer. Data on neuronal density were obtained from counting boxes (50 μm \times 50 μm \times height of section thickness), randomly sampled from each cortical area and layer, as described in detail in a previous study (Dombrowski et al. 2001). The sample size of normative data exceeded the size required by approaches of unbiased stereologic counting (Gundersen et al. 1988). The metric thickness of cortical layers (compartmentalized into layers I, II+III, IV, and V+VI) in 21 prefrontal areas was measured from coronal sections, and relative laminar thickness values were calculated for all layers by dividing the absolute thickness of each layer by the total cortical thickness. Because the orientations of most sulci in the rhesus monkey brain are not orthogonal to the coronal plane, slicing the brain cuts some areas at an angle, resulting in a certain degree of error in the measurement of cortical thickness. However, relative thickness, as well as a magnetic resonance image (MRI) measure for cortical thickness (described below) are unaffected by the potential non-orthogonality of sections. In addition to these measurements, the prefrontal areas were also classified into three groups of predominantly gyral (areas M9, M10, 32, OPro, 13g, D8g, V8g), sulcal (V46r, D46c, V46c, D8s, V8s), or intermediate shape (11, O12, D46r, M14, OPAlI, 24ar, 24ac, M25, 13s). The intermediate category comprised cortical areas of mixed character, or areas that had straight parts as well as a shallow sulcal component. Criteria used to determine areal and laminar boundaries were based on architectonic features (Barbas and Pandya 1989).

The data indicated that the placement of an area in a particular cortical landscape significantly affected both the relative and absolute thickness of layers. Thus, the relative widths of superficial layers (I, II+III, and IV) in all cortices were significantly and positively correlated with each other (average correlation $r=0.73$, $P<0.05$), and they correlated inversely with the relative thickness of the deep layers (V+VI) (average correlation $r=-0.73$, $P<0.05$). This is consistent with tangential forces in gyri stretching the superficial, and compressing and vertically expanding the deep layers (and vice versa in sulci). Interestingly, these data also imply an objective categorization of cortical layers into superficial (I+II+III+IV) and deep (V+VI) layers.

The data also showed a quantitative difference in the absolute thickness of gyral and sulcal regions. This observation was supported by computing the global

distribution of total cortical depth in the rhesus monkey cortex from structural MRI data. The FREESURFER software package was used to reconstruct five individual cortical maps in 3D (Dale et al. 1999; Fischl et al. 1999a), to generate an average template hemisphere and to globally compute the average cortical thickness (Fischl et al. 1999b; Fischl and Dale 2000). The thickness of all surface points was rank-correlated with a transform variable which indicated the relative gyral or sulcal character of the vertex. This analysis showed a significant if moderate correlation between increasing gyral character and absolute thickness across the whole cortex ($\rho=0.36$, $P=0.000001$). A closer investigation of the more detailed prefrontal structural data revealed that the greater absolute thickness of gyri was specifically due to an increase in the thickness of the deep layers (V+VI, Fig. 1).

Since the density of deep cortical layers is relatively invariant across gyral, straight and sulcal regions (Dombrowski et al. 2001), the increased thickness of deep gyral layers also indicated an increase of the total number of neurons in these layers (Fig. 2). Indeed, this increase was so large that cortical columns (under 1 mm^2 of surface and extending through the whole cortical depth) had significantly more neurons in gyral areas than cortical columns in non-gyral areas (one-tailed t test, $P<0.03$). This finding challenges the traditional belief that the number of neurons in a cortical column is constant across different cortical areas (Rockel et al. 1980).

Cortical folding and neuronal migration

What is the reason for the significantly greater number of neurons in deep gyral layers? We suggest a developmental explanation. Developmental studies indicate that the 'inside-out' formation of cortical layers by radial

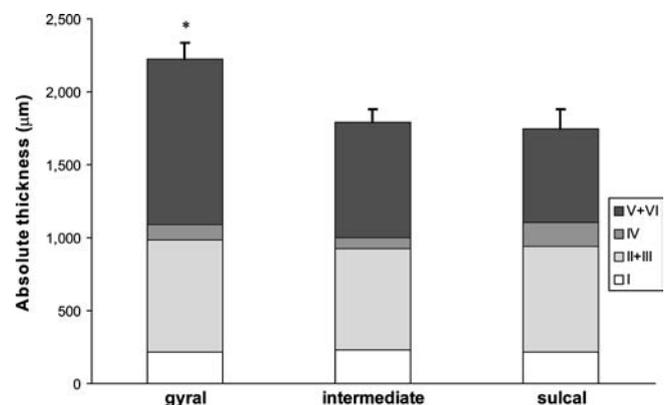


Fig. 1 Absolute laminar thickness in different parts of the cortical landscape. Deep cortical layers are placed at the top and superficial layers at the bottom of the bars. The increase in total gyral thickness is specifically due to a significant increase in the width of the deep cortical layers ($P<0.01$)

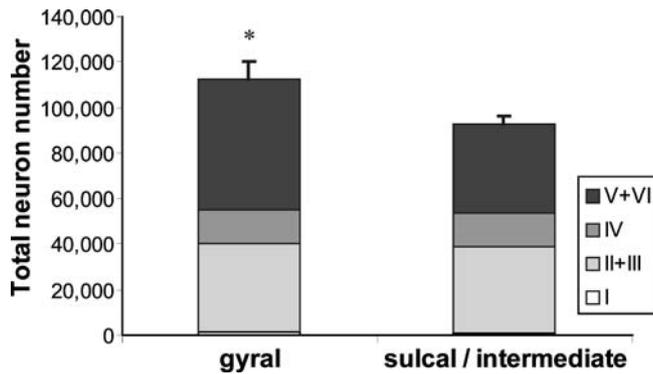


Fig. 2 Absolute number of neurons in a cortical column (under 1 mm² of cortical surface) in gyral and non-gyral regions. The significantly greater number of neurons in cortical columns in gyral regions (one-tailed *t* test, $P < 0.03$) specifically results from the increased number of neurons in the deep layers ($P < 0.002$). There exists a close relationship between increased neuron number and increased thickness of the deep gyral layers, because the neuronal density of deep layers is relatively invariant across the cortical landscape (Dombrowski et al. 2001)

migration partly overlaps with the folding of the cortical sheet. During gestational week 20 in humans, for instance, primary convolutions are already formed (Chi et al. 1977), while about 20% of the neurons still have to migrate into their target layers (Marin-Padilla 1992). This late migration particularly concerns cells destined for superficial layers, which are subjected to mechanical folding forces as they pass through the intermediate cortical layers. In gyri, these forces would tangentially compress the intermediate layers, creating additional mechanical resistance to vertical migration and potentially arresting neurons in the deep layers. In contrast, the intermediate layers might be expanded in sulci, potentially facilitating migration.

The normative structural data (cell density and cortical thickness as described in the section on ‘Relative and absolute laminar thickness’, above) support this hypothesis. There were significantly more neurons in layers V+VI of gyral areas than in intermediate areas, and more neurons in the deep layers of intermediate than sulcal areas (pairwise *t* tests, Bonferroni-adjusted, $P < 0.05$). In line with this explanation, a greater curvature of gyri should increase tangential pressure and, thus, the mechanical resistance to vertical migration of neurons. This, in turn, should result in a higher number of cells, and greater cortical thickness, in the more strongly curved convolutions. Consistent with this prediction, a recent morphometric study found a perfect positive correlation between gyral curvature and cortical thickness of normal as well as schizophrenic human subjects (White et al. 2003). Direct experimental support for our hypothesis that mechanical forces differentially affect the destination of migrating cells in gyral and sulcal layers may come from studies using neuronal birthdate labeling (Sidman and Rakic 1973).

Neuronal morphology and function

As noted previously (Bok 1959; Van Essen 1997), the mechanical impact of cortical folding extends to the finer morphologic features of the cerebral cortex, affecting cellular and dendritic shape, as well as the layout of cortical blood vessels (Miodonski 1974), in different layers. These effects were evident in prefrontal cortices in all cases ($n = 7$) used to study normative structural features. We present an example (Fig. 3) to demonstrate the differential mechanical impact on somata and arbors of pyramidal neurons residing in deep cortical layers of the prefrontal arcuate sulcus. Even though the depicted neurons reside in the same cortical region and in the same layer, somata and arbors of neurons in the deep layers of gyri are clearly stretched radially (Fig. 3b). In contrast, neuronal somata in the deep sulcal layers are compressed tangentially and their apical dendrites are wavy (Fig. 3d).

Modified physiological properties of neurons resulting from different neuronal morphology have been investigated experimentally and computationally in terms of dendritic size and complexity (reviewed in Krichmar and Nasuto 2002). Are there also functional consequences of the mechanical transformations, such as stretching and compression, associated with the respective placement of neurons in gyral and sulcal regions? We investigated the physiological properties of model pyramidal neurons before and after such morphological changes, using the neuronal simulation environment NEURON v.5.5 (Hines and Carnevale 1997), <http://www.neuron.yale.edu/>. The program models neuronal physiology by applying cable theory to passive dendritic sections and computing the integration of depolarizing and polarizing potentials in the somatic compartment by Hodgkin–Huxley equations. Using a model pyramidal cell, we investigated the electrophysiological consequences of elongating or shortening the apical dendrites, in line with the cell’s putative placement in gyral or sulcal regions.

Given the increased absolute thickness of gyral regions, pyramidal neurons in such cortices form longer apical dendrites to reach layer I than neurons placed in the same layer in sulcal regions. Studying a comparatively simple model neuron supplied with the simulation software (3D-reconstructed neocortical pyramidal cell provided in the NEURONDEMO package), we doubled the length of apical dendritic segments, and tested the neuronal responses of the original (‘sulcal’) and the stretched (‘gyral’) neurons to current pulse injections in the same dendritic segments (pulse duration 0.5 ms, amplitude 10 nA). The simulations demonstrated that the otherwise identical neurons which only differed in the length of their apical segments had a different capacity for producing action potentials (Fig. 4). Unless the apical dendrites of pyramidal neurons in gyral regions are proportionally thicker than the ones in sulcal regions, the elongation of the gyral dendrites results in a greater attenuation of excitatory postsynaptic potentials

Fig. 3 Mechanical impact on cellular morphology. **a** Low magnification overview of coronal section through the lower limb of the arcuate sulcus in the rhesus monkey prefrontal cortex. *Scale bar* 500 μ m. Tissue was processed for SMI-32, an antibody to an intermediate neurofilament protein which labels largely pyramidal neurons in cortical layers II + III and V + VI. **b** High-magnification view of layers V and III at the crest of a gyrus, showing elongated dendritic arbors and cell bodies of neurons in layer V (*arrowheads*). **c** High-magnification view of layers V and III in a straight sulcal part of the lower limb of the arcuate sulcus. **d** High-magnification view of layers V and III in the sulcal crease of the ventral limb of the arcuate sulcus showing flattened cell bodies and wavy, tangentially oriented dendrites at the bottom of the sulcus (*arrowheads*). *Scale bar* for panels **b-d** 100 μ m

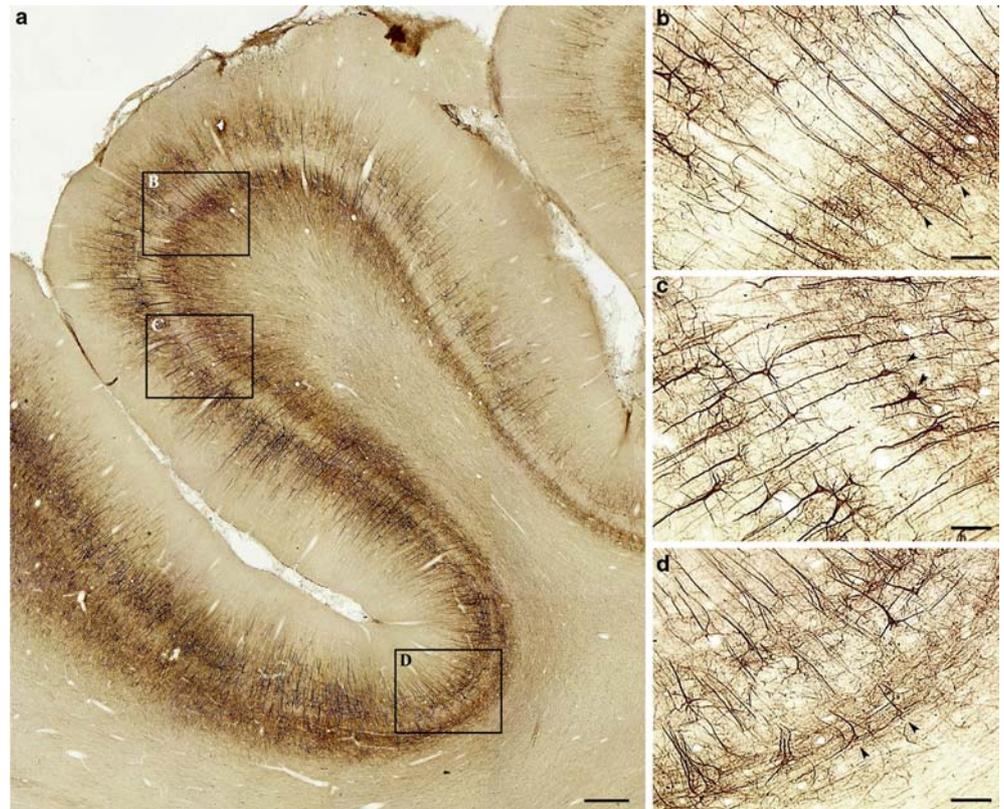
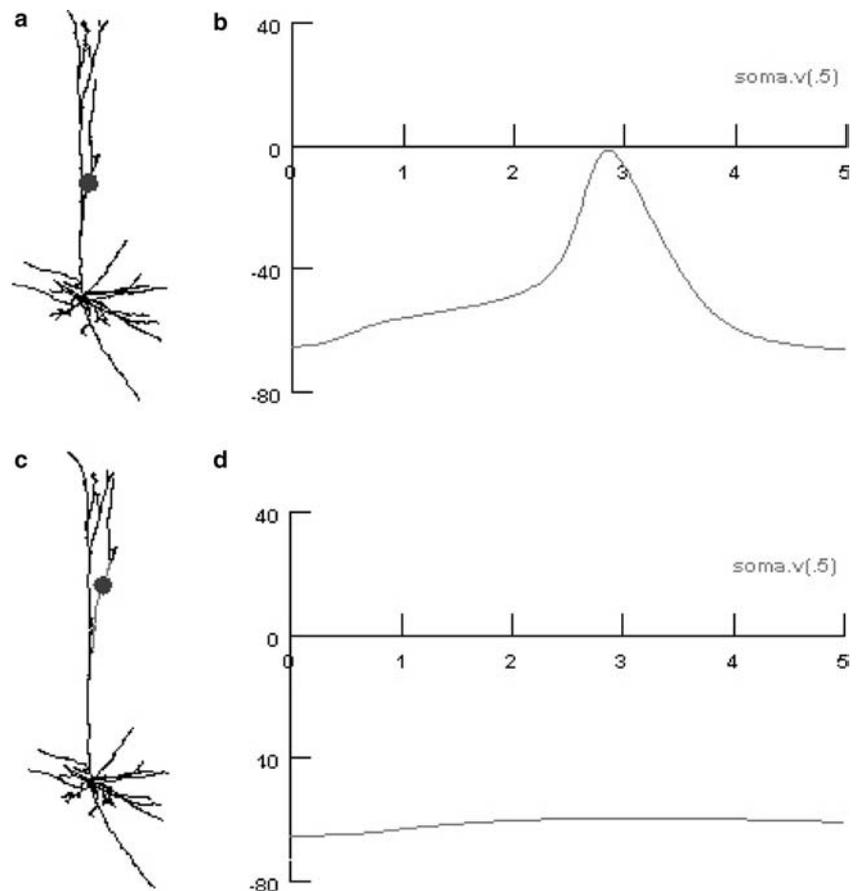


Fig. 4 Impact of neuronal morphology on action potential generation. Simulations were performed in the modeling software NEURON. Cells were stimulated with the same current at the dendritic segment indicated by a dot, and resulting potentials were recorded at the soma. **a** Model pyramidal neuron provided by the NEURON software package. **c** Model neuron with elongated apical dendritic segments. **b, d** Resulting somatic potentials. Due to the greater attenuation of dendritic potentials over the longer segments in the stretched neuron shown in panel **c**, action potentials were no longer elicited



and a potential failure to produce action potentials (Fig. 4). Another way to compensate for the attenuation, however, would be through a greater number of presynaptic inputs or modified synaptic weights. But in this case as well, the modified circuit connectivity implies a different integration of presynaptic potentials, and hence different cellular functioning, in different parts of the cortical landscape. The strong influence of cortical folding on the cellular morphology (Fig. 3) may have further functional consequences. It will be interesting to explore this morphologic impact experimentally, either by electrophysiological recordings from *in vitro* preparations which are mechanically deformed in different directions, or by *in vivo* recordings from equivalent parts of a cortical area that are only distinguished by their gyral or sulcal shape.

Conclusions

It has been suggested that the characteristic convoluted landscape of the primate cerebral cortex is shaped with the contribution of mechanical factors. The results presented here, derived from the analysis of extensive quantitative data for structure and connections of prefrontal cortices, specifically support the hypothesis that the competitive tension exerted by axonal fibers plays a major role in cortical morphogenesis (Van Essen 1997; Hilgetag and Barbas 2002). The idea that the shape of the cortical landscape is determined through a global competition of axonal tension forces is analogous to molecular modeling, where the shape of a molecule is derived through minimizing the total free energy of all its atomic bonds. In a similar vein, the ultimate goal of the axonal tension concept is to relate the specific shape of an individual brain to the arrangement and density of its long-range projections. This would be particularly important for inferring developmental changes of brain connectivity in conditions that produce an abnormal cortical morphology, such as autism (Levitt et al. 2003), Turner syndrome (Molko et al. 2003), and schizophrenia (White et al. 2003). However, it is not yet possible to realize this ultimate goal, for several reasons. The structural connectivity of the human brain is still poorly known, and quantitative databases for the connectivity of other model species are also lacking, particularly with respect to the spatial arrangement of projections. To have such information available at the level of an individual brain will require a revolution in experimental and computational techniques.

However, it is already possible to derive specific hypotheses within the general framework outlined here. For example, in humans the shallower angle between the Sylvian fissure and the base of the brain in the left hemisphere may be produced through tension exerted by the *arcuate fasciculus*, a massive fiber bundle interconnecting the language-related Wernicke's and Broca's

areas. If this tract is denser in the left hemisphere compared with its counterpart on the right side (Büchel et al. 2004), in line with its presumed functional importance in language processing, it may also be straighter, as were the denser projections in prefrontal cortex.

The classical concept of developmental mechanics emphasized the interplay between predetermined ontogenetic features and physical self-organization (His 1874). The picture of brain development that is now emerging from recent studies strongly supports such a concept. Converging evidence reinforces the idea that mechanical factors significantly contribute to cortical morphogenesis, (e.g., Richman et al. 1975; Armstrong et al. 1991, 1995; Van Essen 1997; Hilgetag and Barbas 2002). On the other hand, there is also evidence for a greater correlation of cortical shape among closer relatives (Baare et al. 2001; Thompson et al. 2001). This finding indicates that genetic factors are involved in cortical morphogenesis, but it is not clear how, and at what point, they act. Genetic factors likely specify the timing of neuronal migration within a developmental growth window (Rakic 1995), and determine the density and layout of connections. In turn, these specifications initiate a cascade of mechanical forces as the cortical sheet expands and folds. Consideration of the interplay of genetic and mechanical forces in the formation of the cortical landscape is more parsimonious than invoking genetic factors alone to directly specify the shape of convolutions through tailored growth. The interdependence of genetic and mechanical factors in shaping the cortex suggests that alteration of the timing of neuronal migration into cortical layers would markedly affect cortical convolutions, and may be at the root of a number of diseases of developmental origin, including schizophrenia, autism, and Turner syndrome.

It should be stressed that the outlined developmental events do not proceed in a strict sequence, but are likely to overlap considerably. This is an important realization, for example, for models describing the cellular impact of cortical folding. Previous folding concepts proposed that the cortical sheet was transformed in an isometric way, affecting the shape of neurons, but not their size, relative arrangement, or absolute number in a given cortical volume (Bok 1959). This idea is based on the assumption that convolutions occur after cortical development is completed. However, developmental studies indicate an overlap of cellular migration with cortical folding, suggesting that compression of the intermediate layers in gyri may create mechanical resistance to the migration of neurons into superficial layers. The present results, of a significantly larger number of cells in deep gyral layers support this hypothesis, and challenge folding models based on isometric cortical transformation.

The findings reviewed here underscore the significant contribution of mechanical forces during the epigenetic self-organization of the cortex. They demonstrate that mechanical factors may determine the trajectory of projections and shape cortical convolutions. The results also indicate how such factors affect laminar morphology,

and suggest that they may directly interact with cellular migration during cortical development. Importantly, the outcome of these mechanical processes may substantially influence functional properties of cortical neurons, layers, and areas.

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