

Impact of mechanical factors on primate cortical organization

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Abstract

In addition to genetic control and metabolic regulation, development of the structural organization of the primate brain is constrained by various mechanical forces. Based on the analysis of quantitative data about the structure and connections of primate prefrontal cortices, we present support for the thesis that mechanical factors during development contribute to establishing the layout of cortical regions, to determining the trajectory of projections, and to influencing the shape and density of cortical layers as well as cellular morphology. The impact of the mechanical forces may also substantially influence functional properties of cortical cells and circuits.

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Introduction

The brain, like any other biological object, is subject to mechanical constraints (Thomson 1917). This may be particularly true for the cerebral cortex in primates, a very densely packed sheet of tissue, about three times the size of the inner surface of the skull (Van Essen 1997) that grows and folds in a highly complex manner during brain development. An influence of mechanical constraints in these processes has been assumed for some time, e.g., (Bok 1959). However, during the last decades, the tremendous amount of insights gained into the genetic control of nervous development overshadowed considerations of mechanical factors.

The issue resurfaced with debates about the concept of minimal wiring in the brain. It was suggested that cortical areas are arranged in such a way that the total amount of wiring among them is minimized, e.g., (Cherniak 1994). This could be brought about by long-range connections predominantly linking neighboring areas (Young 1992) or cortices within the same gyrus (Scannell 1997). It was also proposed that these features are causally related to the viscoelastic properties of axons, which would bring together densely linked cortical regions and would allow sparsely connected cortices to drift apart (Van Essen 1997). However, these hypotheses were primarily based on qualitative data and did not consider the actual trajectories of connections. For instance, the study of next-neighbor connections in the primate visual cortex (Young 1992) was performed on the basis of a summary map of the cortex and qualitative (binary) connection data compiled from the anatomical literature. It was therefore not possible to determine whether the connection between any cortical neighbors really represented the minimal linking trajectory (in 3D) between these areas.

In the present study, we set out to explore the impact of mechanical factors on prefrontal organization by linking quantitative data on connection densities with the actual geometry of prefrontal projections. Additionally we analyzed stereologic data on cellular densities and laminar thickness in gyral, sulcal and uncurved prefrontal cortices to identify consequences of the mechanical folding of the cortical sheet.

Methods

In order to establish the relation between the density of connections and the geometry of their axons, 289 quantitative corticocortical connection patterns among prefrontal cortices in the adult rhesus monkey (*Macaca mulatta*) were evaluated, based on 23 cases of retrograde pathway tracer injections. We used the original brain sections to classify all prefrontal projections according to three categories of trajectories: '*straight*', if the connection followed the shortest possible path in 3D; '*intermediate*', if the connection was mildly deflected by, or curved about halfway around, an intruding sulcus; and '*curved*', if the connection was completely bent around a sulcus. In addition, stereologic procedures were used to determine the areal and laminar density of neurons and glia in 21 prefrontal cortices, and to estimate the thickness of cortical layers in these areas. Data were derived from five to seven individual cases for each measure. Criteria used to determine areal and laminar boundaries were based on architectonic features (Barbas and Pandya 1989).

Results

The data analyses revealed a strong correlation between the density of prefrontal connections and the geometry of their projection patterns. Whereas most straight projections were dense, curved projections were primarily formed by sparse connections. Some exceptions could also be found, in which dense projections had a curved trajectory. However, these cases exclusively concerned links between immediate cortical neighbors or cortical areas of the same type (eulaminate or limbic, (Barbas and Rempel-Clower 1997)). It is therefore likely that the correlation between densities and trajectories was produced through the viscoelastic tension exerted by connections during development (Van Essen 1997), thus relating the joint development and density of projections to the layout of the cortical landscape.

Our analyses also showed that the thickness of upper layers I, II-III and IV was strongly positively correlated, but strongly inversely correlated with the thickness of deeper layers V-VI in all areas. Whereas upper layers were laterally stretched and deeper layers compressed in gyral regions, the opposite picture was present in sulcal cortices. Additionally, a greater overall thickness of gyral as compared to sulcal regions became apparent, which could be produced by the higher overall density of (straight) connections in the gyri. Moreover, the mechanical forces resulting from cortical folding affected cellular morphologies, stretching cell bodies as well as arbors radially in gyri, but laterally in deeper sulcal regions.

Lower absolute cell numbers, both for neurons and for glia, in the upper layers of gyral cortices suggested that the compression of deeper gyral layers interfered with the migration of cells during development. Conversely, the absolute number of cells was increased in the deeper gyral layers, due to their greater overall thickness, as well as potentially because cells destined for the upper layers were retained there during migration.

Conclusions

Our findings lend further support to the concept presented by Van Essen (1997) stating that the cortical landscape is created under the constraint of directed tension exerted by long-range axonal projections. This also suggests that the picture of wiring minimization in the cortex, which has been intensely debated (Young and Scannell 1996), arises quite naturally from the

mechanical linkage of densely connected and the separation of sparsely connected cortices. The results further suggest that timing may also be important, as connections might preferentially form between cortices maturing around the same time.

Mechanical forces resulting from cortical folding also appear to play a significant role in determining the morphology of cortical layers and cells in them. These deformations likely affect local connectivity and the functional properties of cortical cells and circuits, since cellular morphologies can be linked to specific functional roles, e.g., (Ferster 1998). It will, therefore, be a challenge for the future to explore the causal relationship between cortical geometry and function in greater detail.

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