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Review

Role of mechanical morphogenesis in the development and evolution of the neocortex

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Abstract

During the short period of brain development, nature is able to build the only system we know capable of producing cognition, language, creativity, and consciousness. The neocortex – the outermost layer of the mammalian cerebrum – appears to be the biological substrate of these abilities. Its development requires not only the precise placement and wiring of billions of cells, but also the implementation of mechanisms to ensure a viable cognition despite sometimes dramatic perturbations. Today, this remarkably complex organisation is thought to be genetically encoded, and further refined by activity-dependent processes. We propose that mechanical morphogenesis – the capacity of homogeneously growing elastic tissue to produce complex shapes – can also play an important role. Out of homogeneous growth, mechanical morphogenesis can induce the segregation of the neocortex into mechanical and geometric modules – the neocortical folds. Through the feedback of physical forces on developing tissue, these modules can influence the differentiation and wiring of the neocortex, having a causal role on neocortical development, and providing adaptable and robust units for its evolution.

Keywords: Neocortical folding; Mechanical morphogenesis; Buckling; Brain development; Brain evolution

1. Introduction

How is the remarkable complexity of the mammalian neocortex produced? From mice to whales, mammalian neocortices are a relatively thin layer of neuronal bodies, differentiated into a series of interconnected cytoarchitectonic fields. Neocortical surface area is extremely variable across species, from about 1.5 cm^2 in mice, 1,500 cm^2 in humans, to 3,000 cm^2 in pilot whales [34]. Its thickness, by contrast, only varies from about 1 mm in mice to 2.5 mm in humans. In the direction of its thickness, the neocortex can be divided into 6 main layers. The connections among those layers tend to follow a canonical circuit: neurones in layer 4 receive connections from subcortical structures, project to those in the superficial layers which then send projections to other neocortical areas and to the deep layers below

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layer 4. Neurones in deep layers mostly send projections to regions outside the neocortex [12,14]. Variations in layer thickness, presence of sub-layers, neuronal morphology, intracortical myelination, but also connectivity, chemical receptor distribution and gene expression, allow us to distinguish different neocortical regions – the cytoarchitectonic areas. Some of these areas exhibit well described relationships with sensory and motor functions. For example, the primary visual cortex or V1, located in the posterior part of the brain, contains a complete "retinotopic" map of the visual field: neighbouring locations of the eye's retina occupy neighbouring locations in V1. Furthermore, different cell types in the retina project to different sublayers of V1's layer 4, and these connections are segregated into ocular dominance bands preferentially related to the left or the right eye. V1 has connections with various other visual areas that have been related to several other aspects of visual perception, as well as with associative areas combining multiple sensory modalities [14].

An interesting observation, dating from the first brain cartography studies at the beginning of the 20th century, is the puzzling relationship between the cytoarchitectonic organisation of the neocortex, its connections and functions, with the geometry of its sulci and gyri – the valleys and hills of the cerebrum [5]. Many examples of this relationship exist. In humans and other primates, a deep fold called the central sulcus separates the somatosensory cortex from the motor cortex. In the primary visual cortex, another deep fold, the calcarine sulcus, separates the superior and inferior visual hemifields. Experiments in animals such as ferrets or racoons show that sulci in the somatosensory cortex often appear silent in electrophysiological recordings, whereas gyri readily respond to sensory stimulation of different parts of the body [30,42,58]. In addition to these cytoarchitectonic and functional differences, brain connectivity also shows a relationship with sulco-gyral anatomy. For example, a ubiquitous type of short association fibres, the U-fibres, connect regions in neighbouring gyri: axonal fibres are perpendicular to the neocortical surface in the top of gyri, but tangential in the bottom of sulci [6,8,51].

2. Genetic and activity-dependent processes

There is agreement today that the development of neocortical organisation follows a genetically encoded template, a protomap, refined by activity-dependent processes [28,37–39,41]. A series of experiments in mice suggest that the general layout of the neocortex is deployed through the establishment of molecular gradients from a reduced number of patterning centres. Through these gradients, each neocortical location would be characterised by a unique combination of molecules, which would then trigger the development of a specific type of cortex [37]. For example, the experimental alteration of the gradient of one of these molecules – the transcription factor EMX2 – produces the displacement of the mouse barrel cortex (the neocortical region that responds to the stimulation of individual whiskers), and even its duplication [18,23]. The global coordinate system produced by molecular gradients would then allow the local specification of cytoarchitectonic areas and their connections: each region would be genetically programmed to attract specific types of connections, and produce fibres aiming to connect with specific targets. Further refinement of this layout would then be achieved through activity-dependent processes, such as visual stimulation. For example, it has been observed that ocular dominance bands fail to develop if visual activity is prevented [10,26]. More impressively, experiments in mice, hamsters and ferrets where visual connections were made to innervate the auditory cortex showed that visual activity was able to induce a cytoarchitecture in the auditory cortex that resembles strikingly that of a normal visual cortex [36,46,48].

Most support for the idea of a genetic encoding of neocortical organisation comes from experiments in mice, which are at the lowest extreme of mammalian brain size, have a comparatively small number of cytoarchitectonic fields, little cortico-cortical connectivity, and no neocortical folding. It would be nevertheless easy to extend the principle to encompass cases of more complex neocortical organisations. We could imagine that mammals with larger neocortices also evolved a more complex genetic decoding mechanism from global molecular coordinates into cytoarchitectonic regions and cortico-cortical connections.

We could also easily extend this idea to explain the correspondence of cytoarchitectonic and connective organisation with sulci and gyri: the same genetic program that determines the specification of different areas and their connections, could also encode the pattern of brain folds. Several hypotheses about the way in which this could be implemented have been indeed proposed through the years. For example, it has been proposed that the tension along axons connecting different regions could make the neocortex fold, explaining the relationship between folding and connectivity [56]. It has also been proposed that the genetic protomap could encode the differential growth of some areas [43], either by driving gyral regions to grow more [11,57] or by preventing sulci from moving [47].

However, we will now review recent theoretical and experimental results which suggest that brain folding is an autonomous process, and that neocortical growth on top of the elastic white matter substrate should be sufficient to produce cortical folding. If this is indeed the case, the current idea of a genetic prescription of neocortical organisation may have to be reviewed: An explanation of the relationship between cytoarchitectonic/connective organisation and the sulcal/gyral anatomy may need to take mechanical instabilities more fully into account. The potential implications are very important because brain folding, which was supposed to be an effect, could turn out indeed to be a cause.

3. Mechanical morphogenesis

Brain tissue, grey and white matter, has mechanical properties similar to those of jelly: it is elastic, and largely incompressible [21,49]. During development, the neocortex is formed by the accumulation of successive waves of neurones migrating from the inner core of the cerebrum – the ventricular and outer subventricular zones [40]. After the end of neuronal migration the cerebral hemispheres are still smooth (unfolded) and neurones are densely packed. The growth of intracortical connections, dendritic trees and glial proliferation then produces a rapid neocortical expansion. In humans, the neocortex is still unfolded at 20 weeks of gestation, and expands from $\sim 80\ \text{cm}^2$ at that time to $\sim 600\ \text{cm}^2$ at birth, when it is profusely folded – a 7.5-fold increase in surface area [13,19]. During the equivalent period in ferrets, from postnatal day 0 until 1 month of age, the neocortex expands 10-fold, from $\sim 3\ \text{cm}^2$ to $\sim 30\ \text{cm}^2$ [27]. Results from soft matter physics show that folds, wrinkles, ridges and creases, are the expected outcomes in such systems [22]. An elastic layer such as the neocortex, growing on top of an elastic substrate such as the white matter, will first grow without folding; but if growth continues, the cost of bending the neocortex will become energetically less than that required to keep expanding the white matter, leading to folding. Several models of brain folding have been built on this principle [1,3,49,52]. These models are able to reproduce the dynamics of brain folding, their shape, the degree of folding of brains as a function of their size, and even the differences in thickness characteristic of sulcal and gyral regions. They show that even some aspects of the pattern of neocortical folding – the locations where they form – could be explained by mechanical and geometrical properties [49,50,52,54].

The mechanical formation of folding should induce, in addition to the large geometric deformation of the tissue, a complex pattern of stress gradients at the scale of the complete organ [16,22,35]. Developing tissue is very sensitive to its mechanical environment [17]. The feedback of stress gradients onto biological tissue could trigger a variety of responses. *In vitro* experiments show that mechanical forces can modulate cell proliferation and programmed cell death [33,44]. Differences in substrate stiffness can determine whether neuronal progenitors produce glial cells or neurones [44]. Softer substrates have been observed to promote neuronal dendritic branching [15]. Axons tend to follow the stiffer directions when cultured on a mechanically anisotropic substrate [45]. The type and range of mechanical forces that can be studied in cell cultures is, however, limited and often non-physiological. Karzbrun et al. [25] recently introduced a methodology to produce growth-induced mechanical folding in cerebral organoids – three-dimensional cell cultures able to mimic several aspects of brain development and organisation [29]. This approach may provide in the future a strategy for studying a much richer variety of effects of mechanical morphogenesis on tissue organisation.

Without requiring a genetic prescription of neocortical organisation, the formation of brain folding could induce a stable and complex pattern of regional cellular changes and neuronal connections. Together with genetic and activity-dependent processes, mechanical morphogenesis, and in particular brain folding, could play an important role in the development and evolution of neocortical organisation.

4. Testing mechanical morphogenesis

While there is a variety of methodologies for probing the causal effect of activity-dependent and genetic processes, no equivalent method exists today for testing mechanical morphogenetic processes *in vivo*. Perturbation methodologies such as sensory deprivation, enucleation of the eyes, activity blockade, optogenetics, gene knockouts, knockins, localised electroporation or CRISPR gene-editing, allow researchers to study the effects of neuronal activity and genetics on brain development. Moreover, through the years, the relevant methods have also been developed to control for unwanted side effects of these interventions such as inflammation or toxicity. Probing the role of mechanical morphogenesis on the development of folding and neocortical organisation requires similar methodologies to introduce a perturbation while controlling for undesired side effects.

A few examples of mechanical perturbations of brain folding exist in the literature. Barron [2] studied the role of the constraint imposed by the cranium on brain folding in developing sheep. As many herbivores, sheep have a rather thin and profusely folded neocortex. Barron surgically extracted *in utero* up to one complete hemisphere. If the brain folds because of the limited intracranial space, the remaining hemisphere should be able to grow unconstrained, and thus unfolded. On the contrary, he observed at birth a degree and a pattern of folding of the remaining hemisphere very similar to those of normal sheep. Welker [57] aimed at testing the possibility of altering an already established folding pattern in cats and racoons. Removing a large portion of the neocortex in cats, he was able to change the anterior–posterior course of many folds into an orthogonal inferior–superior direction. In racoons, he removed most of the white matter inside the temporal lobe. Released from the white matter, the neocortex lost its folds [57].

The experiments of Barron [2] and Welker [57] were extremely invasive, and the knowledge gained from mathematical modelling should help us design less invasive, more reproducible methodologies. If brain folding results from a mechanical instability, then the neocortex should be at a maximally unstable configuration by the time immediately preceding the formation of the first folds. Mechanical models suggest that the initial neocortical geometry strongly regulates folding pattern, and can be used to predict the most likely orientations in which folds will develop [4]. These orientations have been suggested to correspond to the principal directions of curvature of the surface – the two orthogonal directions at each point of a surface where mean curvature reaches its minimum and its maximum [49,50,54]. At the time immediately preceding gyrification, even a small perturbation introduced at the right location should suffice to trigger the development of a fold. Ferrets have become important animal models for the study of brain folding, in particular, because brain folding starts in ferrets during the first few days after birth (in humans folding starts during the last trimester of gestation). A mechanical perturbation could be introduced surgically in a ferret kit, for example, by implanting a soft rod between the cranium and the neocortical surface. However, a completely non-invasive perturbation could be performed, for example, using ultrasonic technology. Acoustic radiation force [20] can produce forces strong enough to levitate and manipulate small objects without contact, and can be maintained for many hours without damaging the tissues. The skull of ferret kits is still thin, and ultrasonic stimulation should not require surgical interventions. Ultrasonic tomography could also be used to monitor *in vivo* the structure, vascularisation and mechanical properties of the tissue. Ultrasonic recordings could be carried out longitudinally, to monitor the evolution of the experiment without further intervention.

A successful mechanical perturbation should allow us to observe the effects of geometric changes and residual stress gradients on brain organisation, and potentially even on behaviour. If the orientation of brain folding follows indeed one of the two principal directions of curvature, it should be possible to force the selection of the second one: regions folded along the anterior–posterior orientation should fold in the superior–inferior direction (as hinted by the experiments of Welker [57]). In ferrets, various sulci limit cytoarchitectonic and functional fields. If mechanical morphogenesis played a role in this organisation, these boundaries should transform along with the sulci. Several neighbouring gyri in ferrets are connected through U-shaped short fibres. Altering the orientation of brain folding should also alter this pattern, leading to the connection of regions that have never been connected in normal animals. Subcortical structures such as thalamic nuclei are preferentially connected to specific gyri, in particular, those related to different sensory-motor modalities. An altered folding pattern should also change the cortico-subcortical connectivity, with measurable behavioural consequences. In the case of rewired mice and ferrets, for example, where visual activity was made to innervate auditory cortex, some of the characteristics of auditory conditioning were transferred to visual conditioning [32,36].

5. Discussion and conclusion

Mechanical morphogenesis could play an important role on the development and evolution of neocortical organisation. Instead of a detailed genetic prescription of neocortical areas and their connectivity, the growth of the neocortex over the white matter should suffice to trigger the formation of residual stress gradients at the scale of the complete cerebrum, as well as localised modules with prototypic geometry and mechanical properties – the neocortical folds. This could spark a series of responses in the developing tissue, transforming mechanical modules into cytoarchitectonic, connective and functional modules. For the moment we can only speculate about the breadth of the effects that mechanical morphogenesis can have on the developing neocortex *in vivo*, based on results largely obtained *in vitro*. The design of appropriate in vivo mechanical perturbation methodologies is a major challenge for future research.

Mechanical models suggest that the main determinant of the wavelength of folding is neocortical thickness, which is remarkably stable across mammals. As far as total cortical thickness stays unchanged, brain folds should conserve their geometry and the residual stress patterns they produce. This provides a stable, resilient, scaffold for the developmental processes influenced by folding, as well as a reproducible unit over which evolution can operate. Mechanical models of folding predict that wavelength λ should be directly proportional to neocortical thickness t [1,49]. If the elasticity of the grey and the white matter were comparable, then $\lambda \sim 4.4t$ [49]. We have recently studied the variation of fold wavelength in 33 primate species [24]. From vervet monkeys to humans, the wavelength was of 12 mm ± 20% (in close agreement with the mechanical model prediction) despite an 18-fold variation in brain volume.

Evolution requires structures able at the same time to change and adapt, but also sufficiently stable to conserve their fitness [9]. Such “evolvable” structures should be stable for pathological variation, but unstable for physiological variation. Conrad [9] suggests that this can be achieved through compartmentalisation – the creation of relatively independent modules, and component redundancy – the development of repeated modules with similar characteristics. These structures should be produced through multiple independent evolutionary paths so as to ensure their robustness [9,31]. The modules created by brain folding fulfil the characteristics of an evolvable structure: they provide a mechanism to create a series of independent units with similar properties. Their formation can be controlled by a single, strongly polygenic parameter, neocortical growth. Variations in neocortical growth in humans have been shown to be extremely polygenic, resulting from the additive combination of large numbers of small effects [7,55,59]. Whereas the differences in fold wavelength are extremely small, there is a 2-fold inter-individual variation in total cortical surface area and hence in the degree of folding [53]. Modules regulated by brain folding should be then both resilient to a large number of genetic variations affecting neocortical growth, but able to produce an increased number of redundant anatomical units across species, and even within species, without requiring major changes in genetic architecture.

Within this framework, the role of genetic processes would not be to completely encode neocortical organisation up to the level of the individual fold, but to select, regulate and consolidate the variety of developmental patterns that mechanical morphogenesis makes available. Instead of a precise prescription of neocortical regions, a global regulation of neocortical growth should lead to the formation of a series of complex cytoarchitectonic, connective and functional modules. Through activity-dependent processes, these patterns of differentiation and connectivity could be refined to match functional and environmental requirements. In addition to global neocortical growth, a finer control of mechanical morphogenetic processes could be exerted by producing gradual changes in growth rate and timing, or by controlling the developmental processes sculpting the shape of the telencephalon before the onset of neocortical folding. Mechanical morphogenesis could then generate robust and reproducible mechanical modules, providing a physically buffered substrate for development and evolution of the neocortex.

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