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Mechanical forces in cerebral cortical folding: A review of measurements and models

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ABSTRACT

Folding of the cerebral cortical surface is a critical process in human brain development, yet despite decades of indirect study and speculation the mechanics of the process remain incompletely understood. Leading hypotheses have focused on the roles of circumferential expansion of the cortex, radial growth, and internal tension in neuronal fibers (axons). In this article, we review advances in the mathematical modeling of growth and morphogenesis and new experimental data, which together promise to clarify the mechanical basis of cortical folding. Recent experimental studies have illuminated not only the fundamental cellular and molecular processes underlying cortical development, but also the stress state and mechanical behavior of the developing brain. The combination of mathematical modeling and biomechanical data provides a means to evaluate hypothesized mechanisms objectively and quantitatively, and to ensure that they are consistent with physical law, given plausible assumptions and reasonable parameter values.

1. Introduction

The folded shape of the human brain allows the cerebral cortex, the thin (2–4 mm) outer layer of neurons and their associated processes, to attain a very large surface area (~1600 cm^2) relative to brain volume (~1400 cm^3). Cortical folding, or gyrification, is critical to human brain development and function. Abnormal cortical folding has been associated with cognitive or emotional problems, including severe retardation, epilepsy (Pang et al., 2008), autism (Hardan et al., 2004; Nordahl et al., 2007) and schizophrenia (Csernansky et al., 2008a; Harris et al., 2004; Sallet et al., 2003). In humans, cortical folding normally occurs in utero, during the third trimester (Fig. 1).

Large mammals (cows, sheep, whales, dogs) and small carnivorous mammals (cats, raccoons, and ferrets) also have folded brains (Welker, 1990); although rats and mice do not. The ferret is a particularly convenient model in which to study folding because cortical folding occurs post-natally (Fig. 1), roughly between the 5th and 30th days after birth. The development of folds in the ferret brain was described in two seminal papers by Smart and McSherry (1986a, 1986b) who studied the evolution of gross anatomical features of the brain, as well as basic histological changes during this period. The developing ferret brain has also been studied more recently using MR imaging (Barnette et al., 2009; Knutsen et al., 2012; Neal et al., 2007) and more advanced histological methods (Jespersen et al., 2012; Reillo et al., 2011).

Disturbances of cortical folding in humans are clinically important and offer clues to the underlying mechanisms of normal development (Manzini and Walsh, 2011; Pang et al., 2008; Pavone et al., 1993; Richman et al., 1973; Stewart et al.,

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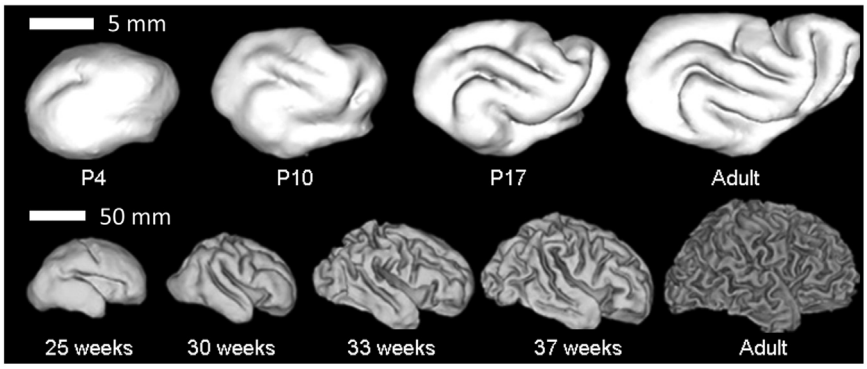

Fig. 1 – Surface representations obtained from MR images of (A) ferret brains at postnatal day 4, 10, 17, and at maturity, and (B) human brains at 25, 30, 33, and 39 weeks gestation and in the adult. Reproduced with permission from Barnette et al. (2009).

1975). Outward, or convex, folds are known as *gyri* and inward folds are called *sulci*. *Lissencephaly* refers to the complete absence of folds, and is associated with greatly reduced numbers of cells in the cortex. *Polymicrogyria* involves numerous small, shallow cortical folds. *Pachygyria* is characterized by a relatively coarse folding pattern, with fewer and larger gyri.

Despite decades of intense study (Barron, 1950; Hofman, 1989; Le Gros Clark, 1945; Welker, 1990) and speculation, the mechanical basis of folding remains controversial. In subsequent sections of this review we briefly describe the basic neurobiology of cortical development, summarize pertinent experimental observations, and discuss the leading theories of folding mechanics.

2. Neurobiology of development

Brain tissue consists of two cell types. Neurons are responsible for conducting electrical impulses and participating in synaptic connections with other neurons, thereby determining the circuitry of the brain. Three primary morphological components of neurons are: the cell body, which contains the cell nucleus; dendrites, which are processes that receive and integrate information from other neurons; and the axon, which conducts electrical impulses from the cell body to other neurons. Glial cells are responsible for other brain functions, including structural roles in directing neuron migration during brain development, and ensheathing axons with myelin to facilitate neural impulse conduction. On the macroscopic scale, brain tissue can be divided into gray matter and white matter. Gray matter, which includes cerebral cortex, primarily consists of neuron cell bodies, dendrites, and synapses. White matter primarily consists of axons and myelin.

Although the timing of onset of cerebral cortical folding relative to the end of gestation varies considerably between species, this variance can primarily be attributed to interspecies differences in the lengths of gestation. With respect to other milestones of central nervous system development, the onset of cerebral cortical folding is consistent between species, and takes place after the majority of cerebral cortical neurons have been born and have completed migration from their sites of origin (cell layers at or near the surface of the lateral ventricle (Rakic, 1995)) to the nascent cerebral cortex, which is termed the cortical plate at its earliest stages of development.

Three notable events that occur simultaneously with cerebral cortical folding are: (i) dramatic expansion of the surface area of the cortex, (ii) morphological differentiation of neurons, which involves extension and branching of axonal and dendritic structures (Fig. 2), and (iii) growth of axon termini from the subplate (a developmentally-transient tissue zone that borders the cortex) into the cortical plate. After the conclusion of these three events, only subtle changes to the shape of the cerebral cortex take place.

Evidence that the process of cerebral cortical folding is linked to brain function underscores the importance of understanding its underlying biomechanics. Congenital brain defects such as lissencephaly, polymicrogyria, and pachygyria are associated with severe mental retardation (Manzini and Walsh, 2011; Pang et al., 2008; Pavone et al., 1993; Richman et al., 1973; Stewart et al., 1975). More subtle abnormalities in cortical folding observed in less severe neurological conditions provide further evidence that the mechanism that drives cortical folding may be linked to the biological source of some neurodevelopmental disorders. In prematurely delivered human infants, cerebral cortical folding abnormalities have been observed, and premature birth is associated with subsequent behavioral and cognitive deficits that become apparent later in childhood (Dubois et al., 2008). Cortical folding abnormalities have also been identified in individuals with Williams syndrome (Van Essen et al., 2006b) and schizophrenia (Csernansky et al., 2008b; Harris et al., 2004; Sallet et al., 2003). In autistic individuals, anomalous cortical folding is observed when compared to age-matched controls (Hardan et al., 2004; Nordahl et al., 2007), and the effect on folding is related to the severity of the behavioral deficit (Nordahl et al., 2007). Collectively, these findings indicate that abnormalities in folding of the cerebral cortex may relate to alterations in brain function.

3. Experimental measurements and observations

The basic question concerning the mechanics of cortical folding is: what forces cause deformation? Is deformation driven by tensile stresses in the interior of gyri (Van Essen, 1997), by growth-driven, tangential compressive stresses in the outer layers of the cortex (Bayly et al., 2013; Richman et al., 1975; Xu et al., 2010), by heterogeneous outward radial growth (Smart and McSherry, 1986a, 1986b), or a combination of these mechanisms? In this