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A physical multifield model predicts the development of volume and structure in the human brain

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Abstract

The prenatal development of the human brain is characterized by a rapid increase in brain volume and a development of a highly folded cortex. At the cellular level, these events are enabled by symmetric and asymmetric cell division in the ventricular regions of the brain followed by an outwards cell migration towards the peripheral regions. The role of mechanics during brain development has been suggested and acknowledged in past decades, but remains insufficiently understood. Here we propose a mechanistic model that couples cell division, cell migration, and brain volume growth to accurately model the developing brain between weeks 10 and 29 of gestation. Our model accurately predicts a 160-fold volume increase from 1.5cm^3 at week 10 to 235cm^3 at week 29 of gestation. In agreement with human brain development, the cortex begins to form around week 22 and accounts for about 30% of the total brain volume at week 29. Our results show that cell division and coupling between cell density and volume growth are essential to accurately model brain volume development, whereas cell migration and diffusion contribute mainly to the development of the cortex. We demonstrate that complex folding patterns, including sinusoidal folds and creases, emerge naturally as the cortex develops, even for low stiffness contrasts between the cortex and subcortex.

Keywords: brain development, cell division, cell migration, volume growth, finite element modeling

1. Introduction

The human brain, amongst that of most other mamallian brains, assumes a highly folded structure throughout its development after being initially smooth. This folded structure offers the great benefit of allowing more surface area for a given brain volume. Indeed, the cortical layer at the brain surface accommodates the cell bodies of the nerve cells that provide the brain with its processing capabilities. Several pathologies in neurodevelopment have been associated with abnormalities in cortical folding and behavioral disorders. A thorough understanding of neurodevelopment is therefore critical towards understanding and, potentially, treating such disorders.

In the human brain, the cortex begins to fold before birth, at around week 24 of gestation [1]. By that time, the brain has already passed several stages of neurodevelopment [2]. Around week 5 of gestation, the stage of asymmetric cell division in the brain begins [3]. This stage is characterized by cell division in the core of the brain followed by outwards cell migration towards the brain periphery. The outward migrating cells begin to form the cortex around week 7 of gestation [4]. The human cortex consists of six distinct layers, with layer 1 on the outside and layer 6 on the inside [5, 6]. This layered structure forms around week 18 of gestation from inside out. That is, layer 6 is formed by the early-born neurons and layer 2 by the last-born neurons. The outer most layer 1 is special as it develops from the marginal zone, which is the outer layer of the brain already present since week 4 of gestation [7]. The cortex differentiates from week 22 of gestation, after which the distinction between white matter in the subcortex and gray matter in the cortex becomes well defined. The cortex begins to fold shortly after, in week 24. The cortex is largely filled with neurons around week 28 when neuronal migration begins to stagnate. The white matter in the subcortex forms axons and matures until 1-2 years after birth [8].

Cortical folding is of critical importance in the developing brain [9]. Various neurological disorders have been directly associated with abnormalities in cortical folding patterns [10]. Polymicrogyria is the phenomenon of many shallow folds and has been linked to delayed development and epilepsy [11, 12]. Lissencephaly, in contrast, is characterized by the absence of cortical folds and may cause several mental disorders [13]. Other folding related diseases are pachygyria, autism, schizophrenia [10, 14].

Two main hypotheses for the development of cortical folding have been proposed [15]. The first hypothesis proposes that axonal tension exerts a tensile pulling force on the cortex which initiates folding [16]. The second hypothesis explains cortical folding as a result of differential growth between the cortex and subcortex that leads to a mechanical instability of the cortex in the form of buckling [17]. Experimental evidence shows that both hypothesis have limitations. First, dissection experiments on ferret brains

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