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DEEP FOLDS IN THE BRAIN RESULT FROM CORTEX PULLING ON ASTROCYTES: A NUMERICAL STUDY

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INTRODUCTION

Our understanding of the process of formation of gyri (hills) and sulci (valleys) in the brain during gestation is moving beyond the role of neurons. Glial cells such as astrocytes are the most prevalent cell type in the brain, especially prominent under the gyri and have been shown to be essential for gyrification [1]. It has also been shown [2] that neural progenitor of glial cells, a subset of which later show astrocytic markers, are preferentially found under regions of prospective gyri. Astrocytic dysfunction has been linked to neurodevelopmental diseases and disorders, leading to abnormal folding patterns, hence it is crucial to understand their role in the mechanics of folding. In this work, we propose two hypotheses that aim to investigate how they affect cortical folding. Literature tells us that astrocytes proliferate and migrate in the white matter (WM), and inhibiting astrocytes impairs gyrification [1]. This leads to the '*pushing'* hypothesis, where astrocytes push up the cortex outwards, leading to formation of folds. On the other hand, ex-vivo studies demonstrate areas of the cortex and subcortex that experience tension [3], due to the differential growth between materials in the brain tissue. This leads to the '*pulling*' hypothesis, where astrocytes experience tension from the surrounding tissue, leading to their proliferation, distribution of tensile stresses, and initiation of growth in those regions. Using the theory of finite growth, we implement these hypotheses via morphogenetic (pushing) and stress-driven (pulling) growth criterions.

METHODS

In this work, the onset and type of growth are inspired by the biological phenomena during ferret gestation. During pre-natal gestation (<P0 days), the concentration of neural progenitors increases, along with increase in volume of the brain tissue. We therefore assume that these progenitors cause growth in the deeper regions of the subcortex, and, that this growth is preferential along locations of future gyri [2]. We design a spatially varying growth rate function (ϕ) that accounts for preferred locations of gyri (Figure 1). After this phase of growth (phase 1), gray matter (GM) starts to grow. Following this, we distinguish the model with two hypotheses. The *pushing* hypothesis uses another spatially varying growth rate function (H) that continues the growth under the preferred gyrus locations as in phase 1. This growth starts at P6 in the simulation because the initial shallow folds are caused by neuronal migration. Moreover, neurogenesis precedes astrogenesis, with astrocytic markers being detected at P0 and their population peaking by P14[4]. In contrast, for the *pulling* hypothesis, the growth from the buildup of tension is captured by the stress-driven growth evolution criterion where tensile stresses initiate astrocyte proliferation and growth, concurrent with GM expansion.

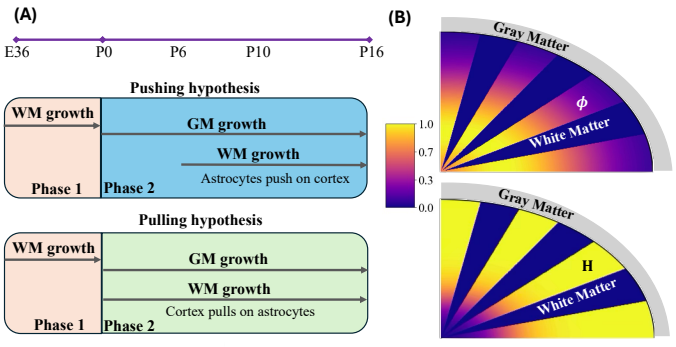

Figure 1: Numerical model. (A)Timeline for the two hypotheses. (B) Functions ϕ and H, used in the growth evolution equations, are shown for the WM.

We use Neo-Hookean materials for GM and WM with shear moduli μ_{GR}

and $\mu_W(=0.5\mu_{GR})$, respectively. Following the theory of finite growth, a kinematic split of deformation gradient is performed,

$$\mathbf{F} = \mathbf{F}^e\mathbf{F}^g. \quad (1)$$

In both hypotheses, growth occurs in an isotropic manner in the WM,

$$\mathbf{F}_W^g = \left(\theta_W^g\right)^{\frac{1}{3}}\mathbf{I}, \quad (2)$$

with the growth $\left(\theta_W^g\right)$ evolution equation for WM in *phase 1* being

$$\dot{\theta}_W^g = G_W^{(1)}\phi(R) \quad (3)$$

where $G_W^{(1)}$ is the growth rate parameter scaled by a Gaussian distribution (ϕ) with R being the radial distance. The GM $\left(\theta_{GR}^g\right)$ is assumed to grow in the plane orthogonal to the outward normal direction **N**

$$\mathbf{F}_{GR}^g = \sqrt{\theta_{GR}^g}\mathbf{I} + \left(1 - \sqrt{\theta_{GR}^g}\right)\mathbf{N}\otimes\mathbf{N} \quad (4)$$

with a constant growth evolution equation

$$\dot{\theta}_{GR}^g = G_{GR}. \quad (5)$$

We assume that $G_W^{(1)} = G_{GR}$. For *phase 2*, the growth evolution equation for WM in the *pushing* hypothesis has another spatially varying growth rate

$$\dot{\theta}_W^g = G_W^{(2)}H(R) \quad (6)$$

where $G_W^{(2)}$ is the growth rate parameter and H is a logistic function. The stress-driven growth evolution equation for WM in the *pulling* hypothesis is

$$\dot{\theta}_W^g = \hat{G}_W^{(2)} < \mathrm{tr}(\boldsymbol{\tau}) > \quad (7)$$

with $\hat{G}_W^{(2)}$ is the growth rate parameter. In the *pushing* hypothesis, $G_W^{(2)}$ is scaled with a scale factor γ such that $G_W^{(2)} = \gamma G_{GR}$. For ease of comparison, in the *pulling* hypothesis, $\hat{G}_W^{(2)}$ is also scaled such that $\hat{G}_W^{(2)} = \hat{\gamma}G_{GR}$, where $\hat{\gamma} = \gamma/\mu_W$.

RESULTS

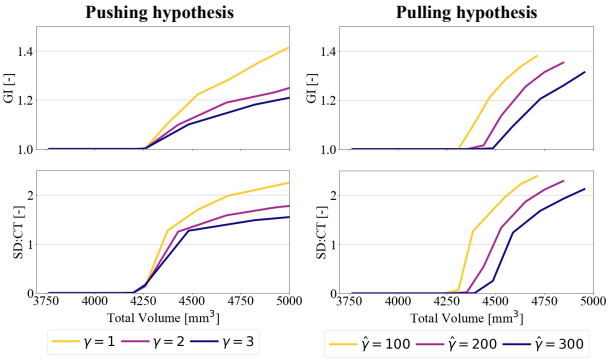

Figure 2: Morphological changes during gestation. The sulcal depth (SD) is normalized with the cortical thickness (CT) to account for changes in both gray and white matter.

Using Abaqus/Explicit and user-defined subroutines for the two hypotheses, the two-phase growth model was setup. The scaling factor γ was varied between 1 and 3, while $\hat{\gamma}$ was varied between 100 and 300. A convex hull was found such that the gyrification index (GI) can be calculated as

$$\mathrm{GI} = \frac{\text{Length of outer contour}}{\text{Length of convex hull}} \quad (8)$$

and sulcal depth (SD) is the depth of the deepest sulcus from the convex hull, with cortical thickness (CT) being the thickness of the GM layer. Figure 2 shows these morphological changes over time with respect to the change in volume. Since we are comparing two distinct growth mechanisms (morphogenetic and stress-driven), variation in volume may occur at different periods of time in both. Hence to compare the two, volume changes are used. Although changes in shape start occurring at lower total volumes in the *pushing* hypothesis, once buckling initiates (after total volume 4200 mm^3), the *pulling* hypothesis has larger normalized sulcal depth. As $\hat{\gamma}$ increases, the changes in GI and SD:CT start occurring at larger volumes but evolve over a smaller range of volume. However, trends from both hypotheses do not provide significant differences and therefore we look at stress distributions in the radial and circumferential directions at points in the white matter (Figure 3). Ex-vivo experiments [3] inform us that areas under the gyri should be under radial and circumferential tension and those under sulci should be under radial compression and circumferential tension. The pushing hypothesis has compressive radial stresses under the gyri as it relies on the pushing effect to cause growth, therefore compressing the subcortex. The second hypothesis leads to tension in both directions under the gyri, while compressing the subcortex under the sulci radially and stretching it circumferentially. Out of the two hypotheses, it is the *pulling* effect that more closely mimics reality.

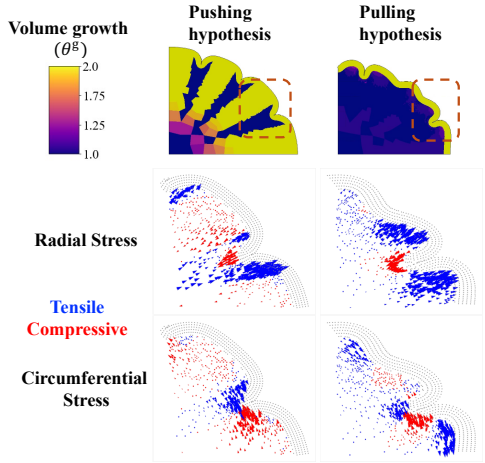

Figure 3: The growth in the simulation for the two hypotheses is compared at P16, along with the radial (σ_r) and circumferential (σ_c) stress distributions in the ROI (dashed box) in the WM.

DISCUSSION

We find that morphological trends during gestation between the pushing and pulling effects are not dissimilar, with comparable gyrification index and sulcal depth metrics. However, the stress distributions from the pulling hypothesis indicate a buildup of tension under gyri, which matches trends observed in experiments [3]. Therefore, it is more likely that the astrocytes affect gyrification by proliferation as a response to tensile cues and decrease the tension they experience, leading to deeper folds, rather than astrocytes proliferating under a gyrus and then pushing the cortex up. This novel study serves as a first step to shed light on the role of these glial cells in the process of gyrification, guiding further ex-vivo and in-vivo studies.

ACKNOWLEDGEMENTS

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