Mechanism Exploration of 3-Hinge Gyral Formation and Pattern Recognition

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Abstract

3-hinge gyral folding is the conjunction of gyrus crest lines from three different orientations. Previous studies have not explored the possible mechanisms of formation of such 3-hinge gyri, which are preserved across species in primate brains. We develop a biomechanical model to mimic the formation of 3-hinge patterns on a real brain and determine how special types of 3-hinge patterns form in certain areas of the model. Our computational and experimental imaging results show that most tertiary convolutions and exact locations of 3-hinge patterns after growth and
folding are unpredictable, but they help explain the consistency of locations and patterns of certain 3-hinge patterns. Growing fibers within the white matter is posited as a determining factor to affect the location and shape of these 3-hinge patterns. Even if the growing fibers do not exert strong enough forces to guide gyrification directly, they still may seed a heterogeneous growth profile which leads to the formation of 3-hinge patterns in specific locations. A minor difference in initial morphology between two growing model brains can lead to distinct numbers and locations of 3-hinge patterns after folding.

**Keyword:** cortical folding; 3-hinge gyri; axon fiber density; differential growth

**Introduction**

Cortical convolution or cortical folding is a prominent characteristic of the mammalian cerebral cortex. They are several studies that have discussed that the study of cortical folding could help us to better understand the normal development of the human brain during the gestation period (Armstrong, Zilles et al. 1993, Harris, Whalley et al. 2004, Duchesnay, Cachia et al. 2007, Geng, Johnston et al. 2007, Wisco, Kuperberg et al. 2007, Fischl, Rajendran et al. 2008, Xintao, Lei et al. 2010, Xu, Knutsen et al. 2010, Zilles, Palomero-Gallagher et al. 2013, Bayly, Taber et al. 2014). Abnormal cortical folding in the fetal stage lead to cognitive or physiological difficulties and problems, e.g. epilepsy, intellectual disabilities and autism spectrum disorder (ASD), and schizophrenia (Kulynych, Luevano et al. 1997, Levine and Barnes 1999, White, Andreasen et al. 2003, Harris, Whalley et al. 2004, Tortori-Donati, Rossi et al. 2005, Kapellou, Counsell et al. 2006, Schaer, Eric Schmitt et al. 2006, Van Essen, Dierker et al. 2006, Nordahl, Dierker et al. 2007, Wisco, Kuperberg et al. 2007, Csernansky, Gillespie et al. 2008, Guerrini, Dobyns et al. 2008, Kennedy and Courchesne 2008, Pang, Atefy et al. 2008, Raybaud and Widjaja 2011, Budday, Raybaud et al. 2014, Sun and Hevner 2014).

Cortical folding has multiple stages: primary, secondary, and tertiary, which all take several months to complete (Sun and Hevner 2014, Budday, Steinmann et al. 2015). Primary folding has been studied very well, while secondary and tertiary folding mechanisms are still quite unclear, leading to a need for more investigations into the development of the developing complex morphology. Primary folding is notably preserved among individuals (Lohmann, Von Cramon et
al. 2008) while secondary and tertiary folding evolve after primary folding is completed, and can vary widely across individuals (Gilles, Leviton et al. 2013). It is believed that differential growth within the cortex is a possible stimulus for secondary and tertiary folding (Richman, Stewart et al. 1975, Tallinen, Chung et al. 2016). According to the tangential differential growth hypothesis, the outer layers of brain show more rapid growth than the inner layers. This growth rate mismatch acts as the driving mechanism for brain structure instability and gyrification. The tangential differential growth hypothesis has been proven by recent experimental and computational analyses (Ronan, Voets et al. 2013, Razavi, Zhang et al. 2015, Razavi, Zhang et al. 2015, Tallinen, Chung et al. 2016), although it is believed that other factors such as axon fiber position and growth also play a nonnegligible role in the regulation of morphology (Holland, Miller et al. 2015, Zhang, Razavi et al. 2016, Zhang, Razavi et al. 2017).

Folding patterns of the human cerebral cortex show quite different morphologies between subjects in secondary and tertiary foldings (Van Essen, Drury et al. 1998, Fischl, Sereno et al. 1999, Liu, Shen et al. 2004). Evidence also has shown that the folding patterns of the human cerebral cortex can predict its cytoarchitecture (Fischl, Rajendran et al. 2008). Therefore, understanding of the underlying mechanism and quantitative description of folding patterns are two important research goals. Before outlining the research subject, it is necessary to define some concepts, e.g., “hinge point”. A hinge point is the point of minimum radius of curvature for a fold, and when these hinge points on a fold surface connect to each other, a hinge line is formed. As shown in Figure 1(a), the hinge of a fold is the field of marked curvature adjacent to the hinge line (Li, Guo et al. 2010). Therefore, we can classify human gyral folding patterns into three classes according to their numbers of hinges: 2-hinge, 3-hinge, and 4-hinge gyri, Figure 1(b). It has been shown in the literature, including our recent work (Li, Guo et al. 2010), that the formation of folding patterns on the cortex at the meso-scale and gyral-scale varies greatly among individuals. Therefore, the number of hinge lines connecting to a field can be used to describe the folding pattern of a hinge field on a gyrus (Yu, Chen et al. 2013). It is noteworthy that the 2-hinge structure is degenerated with the hinge line, and that four gyral crests rarely meet to form 4-hinge gyri (Li, Guo et al. 2010). Thus, we will turn our attention to the most common identifiable structure, the 3-hinge pattern. In contrast to ordinary gyri, gyral hinges are of importance because they have the thickest cortices, the strongest long-range axonal connections and the most pronounced connective diversity, and the most aggregative functional profiles (Ge et al. 2018; Yu et al. 2013; Chen et al. 2014; Jiang et
Moreover, these gyral hinges behave more like cortical hubs in the cortico-cortical networks and compose a majority portion of the network’s “core” (Zhang et al. 2020). Quantitative characterization of gyral folding patterns via hinge numbers with cortical surfaces constructed from MRI data has been used to identify 6 common 3-hinge gyral folds that exhibit consistent anatomical locations across humans, chimpanzees, and macaques, as well as 2 unique 3-hinge patterns in macaques, 6 in chimpanzees, and 14 in humans (Li, Chen et al. 2016). It is not surprising that the number of 3-hinge patterns identified in the human brain is 2.5 and 7.8 times greater than the number found in chimpanzee and macaque brains, respectively. Therefore, the shape and number of 3-hinge patterns in a growing brain could be a new metric to characterize the folding of a primate brain. Interestingly, although there is a direct relationship between the number of 3-hinge patterns and brain size across these three species (human, chimpanzee, macaque), the analysis of number of 3-hinge patterns in other species does not show a clear association between brain size and number of 3-hinge patterns (Li, Chen et al. 2016). In our previous work, we focused on the potential contribution of the dense growing axon fibers to the 3-hinges formation besides the differential growth in white and gray matters. However, it has not addressed the consistency of locations and patterns of certain 3-hinge patterns we have observed in cortical folding. Therefore, there is a critical need to develop a unified biomechanical principle to explain how the intrinsic relationships between cortical folding and structural connection patterns in brains leads to the formation of the observed highly convoluted 3-hinge patterns, and to provide a novel diagnostic for neurological disorders useable during early brain development. As an example, by a comparative MRI study among control group and ASD group in their gyral hinge morphology, we observed that the identified difference in morphology and spatial distribution of 3-hinge patterns of ASD group is associated with the reported functional and cognitive differences (Huang, He et al. 2019). The study helps explain that the gyral hinges could be related to brain functions and used as a potential indicator for diagnostics.

In the present work, we test the hypothesis that the dense growing axon fiber pattern may regulate the patterns of the 3-hinges and help form specific types of 3-hinges and correlate the location, number and shape of 3-hinges with the fiber patterns. We develop a biomechanical model to reveal underlying mechanism of the formation of 3-hinge gyral patterns. The geometrical and mechanical parameters are investigated to understand how these parameters control the number, location, and shapes of 3-hinge patterns. In order to do so, along with the biomechanical model, we develop an
algorithm to automatically detect the number, location and shapes of 3-hinge gyral patterns in in-silico models and in the reconstructed 3D images of real brain. Moreover, we try to elaborate the structural consistency and inconsistency concepts using mechanical simulation to explain the phenomenon where two individuals with globally distinct number and shape of 3-hinges patterns might show certain preserved 3-hinges patterns.

**Computational Models and Methods**

**Constitutive relationship and governing equation of a growing brain model**

Nonlinear finite element simulation accompanied by the theory of finite growth were developed to mimic growth and folding of a developing brain. By implementing the theory of multiplicative decomposition (Rodriguez, Hoger et al. 1994), the deformation gradient $F(\mathbf{X})$ and Jacobian $J$ are decomposed into an elastic element and a growth element. The elastic element describes pure deformation resulting from stresses, and the growth element indicates the addition of materials.

\[
F = A \cdot G \quad (1)
\]

\[
J = \det(F) = J^e J^g \quad (2)
\]

Here, $F = \partial \mathbf{x} / \partial \mathbf{X}$. Points $\mathbf{X}$ from the undeformed configuration are mapped to their new positions $\mathbf{x}$ in the deformed configuration. Although both $A$ and $G$ tensors may be incompatible deformations, their multiplication, $F$, should be a compatible deformation (Ben Amar and Goriely 2005). We assume that growth in the cortex is isotropic and defined by the growth ratio, $g$, in the growth tensor as:

\[
G = gI \quad (3)
\]

\[
J^g = \det(G) = g^3 \quad (4)
\]

Here, $g$ is a scalar. According to our previous works (Zhang, Razavi et al. 2016, Fangfei 2017), we model the material property of the brain with a hyperelastic material incorporating a strain energy function $W(A)$. We characterize the constitutive behavior through the following neo-Hookean free energy equation, parameterized exclusively in terms of the elastic tensor $A$ and its Jacobian $J$.

\[
W = \frac{1}{2} \lambda ln^2 J + \frac{1}{2} \mu [A : A - 3 - 2lnJ] \quad (5)
\]
Here, \( \lambda \) and \( \mu \) are Lamé constants. Following standard arguments of thermodynamics, the Piola stress \( P \) follows as energetically conjugate to the deformation gradient:

\[
P = J \frac{\partial W}{\partial F} \cdot G^{-T}
\]  

(6)

In the absence of body forces, mechanical equilibrium imposes:

\[
\text{Div } P = 0
\]  

(7)

For all parts of the model (white matter, gray matter, and axonal fibers) a similar shear modulus of 0.5 kPa was used (Budday et al. 2015).

**Computational model of a growing brain**

We constructed a three-dimensional (3D) double-layer model as a small piece of the brain to explore the fundamental mechanism of cortical folding and 3-hinge pattern formation, as demonstrated in Figure 2. This model has previously been used to study consistent gyrus formation and also fiber density effect on 3-hinge formation (Ge, Li et al. 2018). Since the main purpose of this study is to investigate mechanisms of 3-hinge pattern formation rather than the effect of the geometry of the model, a flat structure was selected despite the fact that curvature has a considerable effect on convolution patterning (Budday, Steinmann et al. 2015). In the finite element model, a thin top layer represents the cortex (cortical plate). The bottom layer is the core, which is supposed to be a simple representation of the subplate, intermediate zone, and ventricular zone. In human brains, the cerebral cortex is a thin (2–4 mm) layer (Bayly, Taber et al. 2014), in contrast to the core which has a much greater thickness of around 50 mm (Tallinen, Chung et al. 2014). The dimension of the model was selected based on experimental data gathered from small pieces of a brain. The dimension of the base model was 60 mm × 60 mm × 50 mm (not including cortical thickness), and the thickness of the cortex was variable across different models in order to trace the relationship between cortical thickness and the number of 3-hinge patterns. The thickness of the cortex and white matter before cortical folding were set to 1.5 mm and 50 mm, respectively. However, in the study of the effect of cortex’s thickness on the 3-hinge geometrical and mechanical features, the initial cortex’s thickness is set to vary from 1 – 2 mm. Symmetric boundary conditions were applied on four sides of the model and the bottom surface of the core was fixed. The dimension of the model was large enough in comparison with the wavelength of folded patterns observed in experiments so as to prevent boundary effects. In a
bilayer model with an isotropic growth for both cortex and subcortex without stress-dependent growth and no boundary confinement, only their relative growth ratio is a determinant factor for instability and folding. Also in a human premature brain the volume of the cortical plate increases by fourfold in the first two months (22-30 GWs), while the subplate plus intermediate zone (SP+IZ) increases approximately by threefold (Scott et al. 2011). In our recent analytical-computational study, we have already shown that the growth ratio of 4/3 between two distinct layers is sufficient enough to trigger the structural instability (Razavi et al. 2015). This ratio is independent of the growth ratios’ absolute values. Without loss of generality, we set the cortex grow gradually with no growth in the core (Tallinen, Chung et al. 2014, Zhang, Razavi et al. 2016). The growth of the cortex was assumed to be linear in time:

\[ \dot{g}_{\text{cortex}} = g_{ct} \]  

Here, \( g_{ct} \) is a cortex growth constant rate. Previous study has shown that brain growth and folding take place in a long period of time without immediate growth activation (Zöllner et al. 2012). Axonal fibers can elongate under the tensional axial forces as a soft slender structure, but their creep behavior and change in the cross-section by the time due to stress accumulation are not modeled in this study (Lamoureux et al. 2010). We believe that the assumption, namely decoupling the axonal fiber growth from stress state, does not have a considerable effect on the results of the study. Another point is worthwhile to mention that the behavior of axonal fibers inside the surrounding GS might differ from what we can see from the microneedle experiments (Dennerll et al. 1989). Experimental studies (Dennerll et al. 1989; Lamoureux et al. 2010; Bray 1984) have shown that axonal fibers under deformation show a towed growth response (Zöllner et al. 2012), chronic lengthening/shortening to maintain a desired level of axonal tension. However, because cortical folding completes in a long time scale, as the first-order approximation, a nonlinear hyperelastic material model without tension-driven growth has been adopted to study the behavior of the axonal fibers in this study similar to the other micromechanical modeling studies including axonal fibers (Hoursan, Farahmand, and Ahmadian 2020; hoursan, Farahmand, and Ahmadian 2018; Pan et al. 2013; Yousefsani, Shamloo, and Farahmand 2018).

Growth in the model was simulated by thermal expansion (Razavi and Wang 2015, Razavi, Zhang et al. 2015). For further understanding of the analogy between the volumetric growth model and thermal stress model please check reference (Cao, Jiang et al. 2012). By adjusting the thermal
expansion coefficient to the cortex and increasing temperature in dynamic steps, the cortex expands, destabilizes, and then starts to fold. Finite element models were constructed, meshed, and solved using the ABAQUS FE package which is suitable for large deformation, nonlinear, and quasi-static problems. The mesh size was selected as small enough to make qualitative features of the model independent from mesh size. Material properties of the cortex and core were supposed to be same, since there is no substantial difference between gray matter and white matter material properties (Budday, Nay et al. 2015, Tallinen, Chung et al. 2016).

A series of initial small perturbations were introduced into the models to check the effect of initial perturbations on 3-hinge patterns after convolution. Convolution patterns after instability are not guaranteed to be exactly symmetric although the initial model is symmetric (Tallinen, Biggins et al. 2013, Tallinen and Biggins 2015). Applying a small initial perturbation (e.g. displacement perturbation, force perturbation or mech defects) in mechanical models for triggering instability is a common method. There are a lot of studies which have applied small initial perturbations in their growth models for mimicking the biological or mechanical post-perturbation behaviors (Cai, Chen et al. 2012, Cao, Jia et al. 2012, Zang, Zhao et al. 2012, Bayly, Okamoto et al. 2013, Budday, Steinmann et al. 2014, Budday, Kuhl et al. 2015, Wang and Zhao 2015). In our model brain, we apply a small initial perturbation as a trigger of instability after growth. In a real brain, this perturbation could stem from the variation of curvature or heterogeneous growth on distant sites of the brain. The amplitude of the checkerboard perturbation ($\varepsilon_z$) applied in the model brains is one percent of the thickness with a relation as follows:

$$\varepsilon_z = A_0 [\sin(\omega x) + \sin(\omega y)]$$

where, $A_0$ is the amplitude and $\omega$ is the wavelength. The subscript “z” indicates the normal direction to the cortex surface. The $\omega$ in each thirty models are different, so every model has different initial perturbations.

There are two types of growths in axon fiber bundles: a) growth due to mechanical tension, and b) intrinsic biological growth. For the first type of growth, fiber bundles emanate from the base of the model all the way to the interface of the cortex and white matter, which are assumed to be elastic and can grow due to mechanical stress, called the tension-based growth. This tension-based growth in axon fiber bundles depends on the mechanical stress state of cortical foldings and therefore dynamically varies with the stress state changes. With respect to biological intrinsic
growth, we assumed that axon fiber grows along the fiber axial direction and assign a thermal expansion to mimic it (Cao et al. 2012). In this study, we set the biological intrinsic growth to be a constant growth. Growth in axonal fibers is defined as:

$$\dot{g}_{\text{axon}} = g_{af}$$ (10)

where $g_{af}$ is an axonal fiber growth constant rate. Therefore, the growth tensor for the axonal fiber is:

$$G = (g_{axon} - 1)z \otimes z + I$$ (11)

In the models, $z$ shows a unit vector aligned with the axial direction. Increasing the temperature by time causes only the axonal fibers to grow in axial direction.

However, with combined tension-based growth and the intrinsic growth, the resultant growth of axon fiber bundles varies across the entire cortex and along the entire process of cortical folding. As demonstrated in our prior study (Ge et al. 2018), the axon fiber density concentration has been observed to be highest at the hinge point of 3-hinge patterns and decay gradually along the hinge spoke. Therefore, in our model brain we assumed that the hinge junction has the highest axial intrinsic growth with its growth rate being equal to the growth rate of the cortex. $g_{axon}$ is the maximum growth ratio at the 3-hinge junctions accompanied by growth ratios along the hinge lines decaying proportionally from $g_{axon}$ to 0. The growth in the fiber bundles is not isotropic. The hinge lines which include fibers grow only in the axial direction (axial direction is normal to the surface of the cortex). In this study, we also assume that the scaler value of $g_{af}$ of axonal fibers is equal to the $g_{ct}$.

**Brain imaging data and preprocessing**

The Q3 release of Human Connectome Project (https://www.humanconnectome.org) data was used in this study. All HCP subjects were scanned on a customized Siemens 3T “Connectome Skyra”. As we focused on cortical morphology, the white matter surfaces reconstructed from structural MR scans of 868 healthy subjects were of our major interest. Important structural session imaging parameters are listed in Table 1. The white matter surfaces have been produced via the version 3 preprocessing pipelines. Diffusion MRI data was also used to exhibit the distribution of axonal fibers shown. A full DTI session includes 6 runs, representing 3 different gradient tables.
Each gradient table includes approximately 90 diffusion weighting directions plus 6 \( b=0 \) acquisitions interspersed throughout each run. It consists of 3 shells of \( b=1000, 2000, \) and \( 3000s/mm^2 \) interspersed with an approximately equal number of acquisitions on each shell.

The white matter surfaces reconstructed from structural MR scans were provided by HCP dataset by following the structural protocols and data preprocessing pipelines in WU-Minn HCP 900 Subjects Data Release. To produce the fiber density profile from diffusion MRI, we firstly performed skull removal, motion correction, eddy current correction via FSL (Jenkinson, Beckmann et al. 2012, Andersson and Sotiropoulos 2016). The model-free generalized Q-sampling imaging (GQI) method (Yeh, Wedeen et al. 2010) in DSI Studio was then used to estimate the diffusing orientations. Next, the deterministic streamline tracking algorithm in DSI Studio (Yeh, Verstynen et al. 2013) was used to reconstruct \( 4 \times 10^4 \) fiber tracts for each subject using the default fiber tracking parameters (max turning angle=60°, streamline length between 30mm and 300mm, step length=1mm, quantitative anisotropy threshold=0.2). To estimate the fiber density map, we also reconstructed the white matter surface from fractional anisotropic (FA) map of the diffusion MRI. Specifically, FA map was derived from diffusion MRI via FSL-FDT (Jenkinson, Beckmann et al. 2012), first. The FA value quantifies the extent to which water molecules diffuse within a voxel (Beaulieu and Allen 1994, Beaulieu 2002). Next, tissue segmentation (white matter, gray matter and cerebrospinal fluid, CSF for short) was performed on FA map via FSL-FAST (Zhang, Yacoub et al. 2001). Finally, based on the segmentation results, the white matter surface, the border between the white matters and gray matters, was reconstructed via our home-made surface reconstruction toolkit (Liu, Nie et al. 2008). Fiber density was defined as the number of streamline fibers that penetrate a unit surface area.

**Imaging data analysis methods**

In general, 3-hinge data is based on result of gyral net extraction via our recently developed automatic pipeline (Chen, Li et al. 2017). The aim of gyral net extraction is to separate gyral crests from other cortical regions and then skeletonize them to present them as a gyral network. 3-hinge patterns are defined as the joints of such network for which the degree of connection is equal to 3. Briefly, the pipeline consists of two major steps: 1) Gyral crest segmentation: We defined the ‘mid-surface’ as a line that separates gyri and sulci. This ‘mid-surface’ is chosen so that the mean of the displacements of all surface vertices from their original locations is zero. Gyral altitude for a vertex
is defined as the movement from its original location to the ‘mid-surface’ in the surface normal direction, Figure 3(b). Based on these definitions, the watershed algorithm (Bertrand 2005) is adopted to segment the gyral crest (regions over an altitude level, black dots in Figure 3(c)). More details and effects of the watershed algorithm can be found in our previous works (Chen, Li et al. 2017). 2) Gyral Skeleton Extraction: this step is to skeletonize gyral crests, as seen in Figure 3(d)-(e). Gyral skeletons are defined as the crest curves located in the central parts of gyral crest. First, a distance transformation algorithm was conducted on the segmented gyral crests to highlight their central regions. Then, a tree marching algorithm was adopted to successively connect the vertices to form multiple tree-shape graphs. After the redundant branches were pruned, the major branches were left and taken as the skeleton of the gyral crests.

This skeleton can be taken as a gyral network. We defined vertices on this network with degrees more than 2 as gyral joints, red dots in Figure 3(f). Gyral joints with degrees equal to 3 were defined as 3-hinge patterns and are the major interest of this work.

**Detection of location and shape of 3-hinge patterns**

Several FE models with different initial perturbations were run to find geometrical specifications of 3-hinges in a developing brain. Node coordinates of FE models were extracted and fed as input to a MATLAB code to construct a surface of the convoluted model. Then constructed surfaces were fed to a developed algorithm (Chen, Li et al. 2017) to detect numbers and shapes of 3-hinge patterns. Figure 4 schematically shows how the numbers and the shapes of 3-hinge patterns are extracted from the FE models.

**Feature extraction and the shape classification of 3-hinges**

Pipeline for the feature extraction and the shape classification of 3-hinges has been discussed in detail in our previous work (Zhang et al. 2018). For details, such as the rationales and parameter settings are referred to our work by Zhang et al. (Zhang et al. 2018).

**Statistical analysis**

Imaging data results are presented as arithmetic mean averaged over 868 human subjects with no outliers. Least mean square curve fitting method was used to produce the trend lines that fit the data points. Imaging data were analyzed using FreeSurfer and MATLAB (R2015a). Computational data results are presented as arithmetic mean. Least mean square curve fitting method was used to
produce the trend lines that fit the data points. ABAQUS toolkit was used to execute the computational experiments.

**Results and Discussions**

**Formation of 3-hinge patterns in the human brain**

In order to single out the mechanism of formation of 3-hinge patterns in a human brain, we first perform a series of finite element (FE) simulations with homogeneous growth in the cortex. Therefore, a small part of the growing brain is mimicked by a flat bilayer plate model (see Methods section). The reason for considering a small flat patch is that the focus of study is on the underlying mechanism of formation of 3-hinge patterns rather than the effect of brain irregular geometry. Using simple geometry could give basic knowledge regarding growth, folding and formation of 3-hinges in a brain. The thickness of the cortex in the initial state was considered to be 1.5 mm. This number was found based on trial and error so that the average thickness of the cortex after convolution is close to 3.5 mm (the average cortical thickness of a mature human brain)(Bayly, Taber et al. 2014). Figure 5 shows a typical evolution process of the growing brain model and the 3-hinge pattern formation: (a) the cortex gradually grows under a small applied initial perturbation (check Methods Section for details of initial perturbation); (b) instability is initiated on the cortex after a critical growth ratio due to the considerable induced compressive stresses; (c) growth within the cortex after instability leads to folds, producing gyri and sulci; (d) with increasing time and growth, folds become more convoluted and self-contacting folds form 3-hinge patterns. Red points in Figure 5(e) show the locations of 3-hinge centers and the green curves denote hinge lines.

Thirty models with different small initial perturbations were run while all other parameters were kept the same. After computation and post-processing of all models, the number and location of 3-hinge patterns in every model were calculated by the developed algorithm (see Methods section). Results are shown in Figure 6(a) which illustrates that with different initial perturbations, different numbers of 3-hinge patterns form on the cortex. The number of 3-hinges patterns ranged from 29 to 38 and the average number is around 34. Figure 6(b) shows the normal distribution of the number of 3-hinge patterns. The image in Figure 6(c) shows an example case of how our automatic algorithm has detected the locations of the 3-hinge patterns. Results indicate that in all models, the size and thickness of gyri in the hinge lines in 3-hinge patterns are similar to each other, but
locations and shapes can be quite different. The similar variation of locations of 3-hinge patterns can be observed in different individual brains. As an example, Figure 6(d) shows how the locations of major 3-hinge patterns are different in four randomly selected subjects. These results may explain why 3-hinge patterns are notably different across individuals even when they are quite similar in the size and thickness of gyri in the hinge lines. In other words, a very small difference in the initial smooth brain can lead to the formation of considerably different 3-hinge patterns after the development.

In addition to the number of 3-hinges, using the FE data we have also extracted the dominant 3-hinge patterns in order to create a comparison with those observed in the brain imaging data. For the experimental analysis, the dominant 3-hinge patterns and their relative occurrence percentages were extracted from 68 brain subjects with 7,498 detected 3-hinge patterns. For the computational analysis, from the FE models, 844 3-hinge patterns were detected and extracted. Figure 7(a) shows eight dominant shapes of 3-hinge gyral patterns identified in the human brain and FE models. The top numbers (red) and bottom numbers (blue) are the percentages found in real brains and FE models, respectively. This comparison indicates that “Y” shape 3-hinge patterns are the most favorable patterns found in real brains as well as in FE models, although overall the real brain demonstrates more variety in terms of 3-hinge patterns’ shapes. These results show that our biomechanical model, at least partially, can mimic the growth of a brain and capture complex convoluted 3-hinge patterns. With a careful look at Figure 7(a), it can be observed that real brains have certain 3-hinge pattern shapes which our FE models do not capture, although the observed percentage of such shapes is low even in data from real brains. Therefore, there should be other factors that regulate 3-hinge gyral patterns in real brains which are not yet included in our FE models. We will discuss these factors in the following sections. Figure 7(b) qualitatively compares convolution patterns between randomly selected FE models and experimental images. The FE models have different initial perturbations before growth, but all other parameters are the same. The experimental images are extracted from the frontal lobes of real brains. Figure 7(b) indicates that FE models with small initial perturbations develop different convolution patterns. From the mechanical view, as folding process is a dynamic process, final patterns are highly dependent on the initial states and imperfections. Initial small perturbations in the FE model may be analogous to differences in curvature for real brains. This means that different parts of a brain, without considering any other factors and just by attention to their location and curvature, are able to
develop different folding patterns (such as the 3-hinge patterns which are the focus of this work). Moreover, since the initial state of any individual brain is unique to a certain extent, we can expect that tertiary folding patterns are not consistent between any two samples. On the other hand, there are some commonly preserved 3-hinge patterns in all real brains which demonstrate a certain amount of consistency; we thus strive to find an explanation to this consistency.

**Contribution of fibers on the location and the shape of 3-hinge patterns**

In the previous section, we investigated how mechanical parameters are responsible for certain mechanisms of 3-hinge pattern formation. However, those factors alone are not able to determine exact locations and geometry of formed 3-hinge patterns, as shown in Figure 7. Therefore, as discussed previously, there should be other factors which regulate the conserved shape of 3-hinge patterns in a real brain which have not yet been considered in our FE models. In our previous study (Ge, Li et al. 2018), we showed that, in accompaniment with the differential growth theory, growing fibers could possibly control the location of 3-hinge gyrus formation. Figure 8(a) demonstrates that in the real brain, axonal fibers connected to 3-hinge gyral folds are much denser than those found in other areas.

We obtained average fiber densities of brain locations containing 3-hinge gyral patterns and realized that there is a significant difference in the fiber density between 3-hinge gyral folds and the typical gyral crest lines. Therefore, a possible factor which can be incorporated into FE models to explain certain consistencies in location and shape of 3-hinge patterns is the presence and growth of axonal fibers. To do so, we incorporate the role of axonal wiring into the regulation of location and shape of 3-hinge patterns. We created several models with and without growing fibers with gradient growth rates. The assigning gradient growth to fibers considers that the hinge points have higher growth rate than the hinge lines, because the concentration of fibers around the hinge points is highest which decreases over the hinge lines with moving away from the hinge points (see Methods Section for more details). Figure 9 shows a top view of the final state of four FE models without contribution of fibers. All parameters of models except initial perturbation are the same. The 3-hinge patterns (green lines) and their locations (red dots) are different although their qualitative features are similar to each other, which indicates that the differential growth theory by itself only produces 3-hinge patterns in unpredictable locations. We could not find any specific
relationship between the wavelength of the initial perturbation and the location of the formed 3-hinges.

As we observed in Figure 7(a), models without contribution of fibers do not exactly capture 3-hinge patterns and locations same as real images. In the next step, we select two types of 3-hinge pattern from Figure 7 which were observed in real brain and not in FE models, Figure 10(a), (c). We incorporated fibers with gradient growth along the hinge lines following the selected special types of 3-hinge pattern, Figure 10(b), (d). These concentrated bundles of fibers project from the base of white matter to the interface of gray-white matters to mimic higher fiber density on 3-hinge patterns. The axial growth rate of the fibers in the hinge points is considered to be the same as the growth rate of the cortex (Ge, Li et al. 2018). This axial growth rate reduces over the hinge lines linearly to zero at the tip of the hinge lines (gradient growth). Figure 10(e), (g) shows top view of four FE models with growing fibers after growth and convolution. Despite different initial perturbations, we can see that all models form complex 3-hinge patterns which have been observed in real brains. Therefore, growing fibers could be a possible factor to determine or regulate the location and shape of 3-hinge patterns. In our previous study, we set the growth rate of axonal fibers as five different values, all of which are comparable with the growth rate in the cortex. Results showed that there is a very high possibility to form a 3-hinge gyrus in the specific area when the growth rate of axonal fibers is close to the growth rate of the cortex, while the area in models without axonal fibers could be located on hinge, sulci, or in-between banks. In addition, the sites with a high density of growing axonal fibers do not develop any sulci in agreement with the experimental results. This study similar to the other studies (Ge et al. 2018; Chavoshnejad et al. 2021) reveals that although fiber bundles do not induce folding, they can regulate the locations of gyri and sulci.

It is interesting to see that 3-hinge patterns far from their centers are quite different from one another. This result shows that besides the commonly preserved 3-hinge patterns, we can also have various and different 3-hinge patterns in a growing brain such as those illustrated in the previous section. Previous analysis on the relationship between axonal elongation and cortical growth (Holland, Miller et al. 2015) concludes that rather than axons pulling on the brain to induce cortical folding, the folding cortex pulls on the axons to trigger axonal elongation and white matter growth. In our models, we assign axial growth to the fibers. With this assumption before instability and
folding in the model brain, compressive forces appear in the fibers. But, after the gyrification this statement is not true and some of the fibers can feel the tension even if they are growing (mostly fibers in the gyri part). This can happen because the differential growth in the gyrification process is a dominating factor to the axonal growth. Therefore, we observe both tensile and compressive fibers at distant locations.

It is worth noting that only the contribution of fibers has been included in the discussion. Admittedly, the axonal wiring is not the only parameter that control the shape of certain 3-hinges. It is highly possible that axonal wiring together with other factors such as heterogeneity in stiffness and growth and curvature control the 3-hinges number, location, and shape. For example, the initial curvature of the smooth brain has shown a great impact on the morphology of folds (Budday, Steinmann et al. 2015, Tallinen, Chung et al. 2016). Narrow elongated brains tend to fold mainly in the longitudinal direction, while rounder brains, such as the human brain, fold in the transverse direction (Budday, Steinmann et al. 2015). Our previous study also showed that the heterogeneous regional growth in the cortex can produce consistent gyrus in a developing brain (Zhang, Razavi et al. 2016). However, the effect of curvature and heterogeneity in growth and stiffness on the shape and location of 3-hinge patterns in a brain has not yet been thoroughly investigated.

**Effect of the brain size and cortex thickness on the 3-hinge patterns**

So far, we have discussed human subjects, but what are the possible patterns of 3-hinges in other primates? DTI data from 64 HCP human brain specimens revealed that the average number of 3-hinge patterns in a human brain is around 137 (Ge, Li et al. 2018); which is considerably greater than the average number of 3-hinge patterns found in chimpanzee and macaque brains, 108 and 60, respectively (Tuo Zhang 2019). Brain size could be a possible parameter on the number of 3-hinges, in that bigger brains (with higher pre-folding surface area) will have a larger number of 3-hinge patterns. However, results from image data show that different species with similar brain sizes may have a huge difference in the number of 3-hinge patterns (Tuo Zhang 2019). Hence, other parameters may control the number of 3-hinge patterns beyond the brain size. Interestingly, Figure 11(a) shows that even species with the same axis ratio of the brain may not have similar numbers of 3-hinge patterns. The axis ratio is the ratio of major axis of the ellipsoidal shape of brain to the minor axis of it (front to rear distance divided by top to bottom distance). As an example, the brain of both a cat and a lion have similar axis ratios but a big difference in the number of 3-hinge
patterns. Therefore, neither brain size nor axis ratio are singular factors in controlling the number of 3-hinge patterns.

Another possible factor which could be considered is the thickness of the cortex. The thickness of the cortex is different between species and is independent from the size or mass of the brain (Sun and Hevner 2014). The average cortical thicknesses for human, chimpanzee, and macaque brains roughly are 2.5, 2, and 1.68 mm, respectively (Fischl and Dale 2000, Zhang, Razavi et al. 2017). A previous study analytically indicated that the number of folds increases linearly with the ratio of brain radius to cortex thickness (Budday, Steinmann et al. 2015). Although the human brain has a higher cortical thickness, it is more convoluted and has a larger number of 3-hinge patterns. This happens because the human brain has larger surface area and the ratio of brain radius to cortex thickness is higher than in both other primates. In our FE models, the average radii for the brains of human, chimpanzee, and macaque were set as 50, 32, and 26 mm, respectively. Average radius in the patch model is equal to the total height of the model including the thickness of the white and gray matters. Figure 11(b) shows a top view of the FE models for a square patch of every species. The sizes of the patches were selected to be representative of the folding geometry. Figure 11(b) shows that the number of 3-hinge patterns could be a function of cortical thickness. To investigate this relationship, we ran several models for human brains with various cortical thicknesses. The initial cortex thickness varies from 1 − 2 mm. It is worth mentioning that the cortex thickness after growth and convolution is increased compared with the initial thickness.

Figure 12(a) shows the dependency of the number of 3-hinge patterns and final cortical thickness on the initial cortical thickness and the surface area of the cortex. As can be seen, a cortex with a higher surface area has a higher number of 3-hinge patterns, and a thicker cortex has the trend of forming fewer 3-hinge patterns. Figure 12(a) also shows that cortex thickness after convolution has a linear relationship with the initial thickness of cortex. Since the cortical layer after convolution does not have a uniform thickness, being notably different between sulci and gyri, the thicknesses were roughly calculated and averaged in random locations. To calculate the density of 3-hinge patterns in a unit area for all models presented in Figure 12(a), a square patch 6 × 6 cm was cut from the center of models (so as to lessen possible edge effects), and the calculated number of 3-hinge patterns over this area is presented in Figure 12(b). Based on Figure 12(b) we can, with high accuracy, predict how many 3-hinge patterns will form on the cortex with a known initial
cortical thickness and surface area. Furthermore, it is not necessary to have data after convolution; only initial geometrical parameters are required. The human brain in a smooth state, i.e., before convolution, has an average surface area of 120 cm² in 23rd week of gestation (Zhang, Hou et al. 2013) and a cortical thickness of around 1.5 mm. From these numbers, based on Figure 2(b), we can predict that the human brain after convolution will form roughly “142” 3-hinge patterns, which is comparable with the real brain observed average of 137 (Ge, Li et al. 2018). The discrepancy could possibly be from real brain curvature which has not been considered in this model. This result shows that by tuning the initial geometrical parameters in a mechanical model brain, we are able to predict the number of such complex 3-hinge patterns after convolution. The result shows that the role of mechanics on the growth and formation of complex shapes in brain is greater than we previously thought. Future studies are required to help reveal the fundamental contributions of mechanics on the folding of brain and its associated structural disorders.

**Conclusions**

Although mechanical forces play a vital role in the evolution of 3-hinge patterns in cortical folding, the fundamental underlying of these active forces that drive this process remain unclear. By using imaging and computational tools, we set out to identify and study the force-generating parameters which have been included in this complex process. We showed that differential growth along with the presence of axonal fibers could be a potential factor in controlling the number, location, and shape of 3-hinge gyral patterns in a developing human brain. The mechanism of the formation of 3-hinge patterns as a part of cortical folding may involve differential growth in a primary role and axonal wiring in a secondary role. From our study, we can speculate that axonal wiring is one of the main contributors to the formation of 3-hinge patterns with certain unique shapes in designated specific locations, as the differential growth hypothesis does not predict the spatially consistent patterns of certain identifiable 3-hinge patterns. It is a challenging and unanswered question of the complex causal relationship: whether the formation of a 3-hinge pattern then attracts more fibers toward the 3-hinge site, or whether the dense and growing fibers push a specific site to help drive the formation of a 3-hinge pattern initially induced by differential growth. Nevertheless, one clear point is that for the formation of a 3-hinge pattern both differential growth and axonal wiring accompany each other. We also showed that the thickness of the cortex is the main geometrical parameter which determines the number of 3-hinges patterns in a certain brain surface. However,
the size and axis ratio of the brain do not have considerable effect on the number of 3-hinge patterns among different species.

In our work, we choose a small part of the brain with a simple geometry as our basic model to investigate the fundamental of the formation of 3-hinges patterns. This simple model helps us achieve the key findings as we expected, however future studies with a more realistic model brain will be worthwhile to invest for further exploring the details. The effect of the curvature and heterogeneity in growth and stiffness on the formation of 3-hinge patterns could also be studied. Conducting such a comprehensive model may result in the development of an effective tool to diagnose certain common brain disorders such as autism. Therefore, understanding of 3-hinge gyral patterns formation and development can provide useful insight into the differences between normal and pathological brain function.

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Additional Information

Competing financial interests: The authors declare no competing financial interests.

Ethical Statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the University of Georgia and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.
References

Andersson, J. L. R. and S. N. Sotiropoulos (2016). "An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging." *NeuroImage* **125**: 1063-1078.

Armstrong, E., K. Zilles and A. Schleicher (1993). "Cortical folding and the evolution of the human brain." *Journal of Human Evolution* **25**(5): 387-392.

Bayly, P., R. Okamoto, G. Xu, Y. Shi and L. Taber (2013). "A cortical folding model incorporating stress-dependent growth explains gyral wavelengths and stress patterns in the developing brain." *Physical Biology* **10**(1): 016005.

Bayly, P., L. Taber and C. Kroenke (2014). "Mechanical forces in cerebral cortical folding: a review of measurements and models." *Journal of the Mechanical Behavior of Biomedical Materials* **29**: 568-581.

Beaulieu, C. (2002). "The basis of anisotropic water diffusion in the nervous system – a technical review." *NMR in Biomedicine* **15**(7-8): 435-455.

Beaulieu, C. and P. S. Allen (1994). "Determinants of anisotropic water diffusion in nerves." *Magnetic Resonance in Medicine* **31**(4): 394-400.

Ben Amar, M. and A. Goriely (2005). "Growth and instability in elastic tissues." *Journal of the Mechanics and Physics of Solids* **53**(10): 2284-2319.

Bertrand, G. (2005). "On topological watersheds." *Journal of Mathematical Imaging and Vision* **22**(2-3): 217-230.

Budday, S., E. Kuhl and J. W. Hutchinson (2015). "Period-doubling and period-tripling in growing bilayered systems." *Philosophical Magazine* **95**(28-30): 3208-3224.

Budday, S., R. Nay, R. de Rooij, P. Steinmann, T. Wyrobek, T. C. Ovaert and E. Kuhl (2015). "Mechanical properties of gray and white matter brain tissue by indentation." *Journal of the Mechanical Behavior of Biomedical Materials* **46**: 318-330.

Budday, S., C. Raybaud and E. Kuhl (2014). "A mechanical model predicts morphological abnormalities in the developing human brain." *Scientific reports* **4**: 5644.
Budday, S., P. Steinmann, A. Goriely and E. Kuhl (2015). "Size and curvature regulate pattern selection in the mammalian brain." Extreme Mechanics Letters 4: 193-198.

Budday, S., P. Steinmann and E. Kuhl (2014). "The role of mechanics during brain development." Journal of the Mechanics and Physics of Solids 72: 75-92.

Budday, S., P. Steinmann and E. Kuhl (2015). "Secondary instabilities modulate cortical complexity in the mammalian brain." Philosophical Magazine 95(28-30): 3244-3256.

Cai, S., D. Chen, Z. Suo and R. C. Hayward (2012). "Creasing instability of elastomer films." Soft Matter 8(5): 1301-1304.

Cao, Y., Y. Jiang, B. Li and X. Feng (2012). "Biomechanical modeling of surface wrinkling of soft tissues with growth-dependent mechanical properties." Acta Mechanica Solida Sinica 25(5): 483-492.

Cao, Y.-P., F. Jia, Y. Zhao, X.-Q. Feng and S.-W. Yu (2012). "Buckling and post-buckling of a stiff film resting on an elastic graded substrate." International Journal of Solids and Structures 49(13): 1656-1664.

Chen, H., Y. Li, F. Ge, G. Li, D. Shen and T. Liu (2017). "Gyral net: A new representation of cortical folding organization." Medical Image Analysis 42: 14-25.

Csernansky, J. G., S. K. Gillespie, D. L. Dierker, A. Anticevic, L. Wang, D. M. Barch and D. C. Van Essen (2008). "Symmetric abnormalities in sulcal patterning in schizophrenia." Neuroimage 43(3): 440-446.

Duchesnay, E., A. Cachia, A. Roche, D. Rivière, Y. Cointepas, D. Papadopoulos-Orfanos, M. Zilbovicius, J.-L. Martinot, J. Régis and J.-F. Mangin (2007). "Classification based on cortical folding patterns." Medical Imaging, IEEE Transactions on 26(4): 553-565.

Fangfei, R. (2017). "Denser Growing Fiber Connections Induce 3-hinge Gyral Folding." Cerebral Cortex.

Fischl, B. and A. M. Dale (2000). "Measuring the thickness of the human cerebral cortex from magnetic resonance images." Proceedings of the National Academy of Sciences 97(20): 11050-11055.
Fischl, B., N. Rajendran, E. Busa, J. Augustinack, O. Hinds, B. T. Yeo, H. Mohlberg, K. Amunts and K. Zilles (2008). "Cortical folding patterns and predicting cytoarchitecture." Cerebral Cortex 18(8): 1973-1980.

Fischl, B., M. I. Sereno and A. M. Dale (1999). "Cortical surface-based analysis: II: Inflation, flattening, and a surface-based coordinate system." Neuroimage 9(2): 195-207.

Ge, F., X. Li, M. J. Razavi, H. Chen, T. Zhang, S. Zhang, L. Guo, X. Hu, X. Wang and T. Liu (2018). "Denser Growing Fiber Connections Induce 3-hinge Gyral Folding." Cerebral Cortex 28(3): 1064-1075.

Geng, G., L. Johnston, E. Yan, D. Walker and G. Egan (2007). Modelling cerebral cortical folding. Proceedings of Workshop on Computational Biomechanisms, International Conference on Medical Image Computing & Computer Assisted Intervention.

Gilles, F. H., A. Leviton and E. Doolding (2013). The developing human brain: growth and epidemiologic neuropathology, Butterworth-Heinemann.

Guerrini, R., W. B. Dobyns and A. J. Barkovich (2008). "Abnormal development of the human cerebral cortex: genetics, functional consequences and treatment options." Trends in Neurosciences 31(3): 154-162.

Harris, J. M., H. Whalley, S. Yates, P. Miller, E. C. Johnstone and S. M. Lawrie (2004). "Abnormal cortical folding in high-risk individuals: a predictor of the development of schizophrenia?" Biological Psychiatry 56(3): 182-189.

Holland, M. A., K. E. Miller and E. Kuhl (2015). "Emerging brain morphologies from axonal elongation." Annals of Biomedical Engineering 43(7): 1640-1653.

Huang, Y., Z. He, T. Liu, L. Guo and T. Zhang (2019). Identification of Abnormal Cortical 3-Hinge Folding Patterns on Autism Spectral Brains, Cham, Springer International Publishing.

Jenkinson, M., C. F. Beckmann, T. E. Behrens, M. W. Woolrich and S. M. Smith (2012). "Fsl." Neuroimage 62(2): 782-790.

Kapellou, O., S. J. Counsell, N. Kennea, L. Dyet, N. Saeed, J. Stark, E. Maalouf, P. Duggan, M. Ajayi-Obe and J. Hajnal (2006). "Abnormal cortical development after premature birth shown by altered allometric scaling of brain growth." PLoS medicine 3(8): e265.
Kennedy, D. P. and E. Courchesne (2008). "Functional abnormalities of the default network during self-and other-reflection in autism." Social Cognitive and Affective Neuroscience 3(2): 177-190.

Kulynych, J. J., L. F. Luevano, D. W. Jones and D. R. Weinberger (1997). "Cortical abnormality in schizophrenia: an in vivo application of the gyrification index." Biological Psychiatry 41(10): 995-999.

Levine, D. and P. D. Barnes (1999). "Cortical maturation in normal and abnormal fetuses as assessed with prenatal MR imaging." Radiology 210(3): 751-758.

Li, K., L. Guo, G. Li, J. Nie, C. Faraco, G. Cui, Q. Zhao, L. S. Miller and T. Liu (2010). "Gyral folding pattern analysis via surface profiling." NeuroImage 52(4): 1202-1214.

Li, X., H. Chen, T. Zhang, X. Yu, X. Jiang, K. Li, L. Li, M. J. Razavi, X. Wang and X. Hu (2016). "Commonly preserved and species-specific gyral folding patterns across primate brains." Brain Structure and Function 222(5): 2127-2141.

Liu, T., J. Nie, A. Tarokh, L. Guo and S. T. C. Wong (2008). "Reconstruction of central cortical surface from brain MRI images: method and application." Neuroimage 40(3): 991-1002.

Liu, T., D. Shen and C. Davatzikos (2004). "Deformable registration of cortical structures via hybrid volumetric and surface warping." Neuroimage 22(4): 1790-1801.

Lohmann, G., D. Y. Von Cramon and A. C. Colchester (2008). "Deep sulcal landmarks provide an organizing framework for human cortical folding." Cerebral Cortex 18(6): 1415-1420.

Nordahl, C. W., D. Dierker, I. Mostafavi, C. M. Schumann, S. M. Rivera, D. G. Amaral and D. C. Van Essen (2007). "Cortical folding abnormalities in autism revealed by surface-based morphometry." The Journal of Neuroscience 27(43): 11725-11735.

Pang, T., R. Atefy and V. Sheen (2008). "Malformations of cortical development." The Neurologist 14(3): 181.

Raybaud, C. and E. Widjaja (2011). "Development and dysgenesis of the cerebral cortex: malformations of cortical development." Neuroimaging Clinics of North America 21(3): 483-543.

Razavi, M. J. and X. Wang (2015). "Morphological patterns of a growing biological tube in a confined environment with contacting boundary." RSC Advances 5(10): 7440-7449.
Razavi, M. J., T. Zhang, X. Li, T. Liu and X. Wang (2015). "Role of mechanical factors in cortical folding development." Physical Review E 92(3): 032701.

Razavi, M. J., T. Zhang, T. Liu and X. Wang (2015). "Cortical Folding Pattern and its Consistency Induced by Biological Growth." Scientific Reports 5(14477).

Richman, D. P., R. M. Stewart, J. W. Hutchinson and V. S. Caviness Jr (1975). "Mechanical model of brain convolutional development." Science 189(4196): 18-21.

Rodriguez, E. K., A. Hoger and A. D. McCulloch (1994). "Stress-dependent finite growth in soft elastic tissues." Journal of Biomechanics 27(4): 455-467.

Ronan, L., N. Voets, C. Rua, A. Alexander-Bloch, M. Hough, C. Mackay, T. J. Crow, A. James, J. N. Giedd and P. C. Fletcher (2013). "Differential tangential expansion as a mechanism for cortical gyrification." Cerebral Cortex: bht082.

Schaer, M., J. Eric Schmitt, B. Glaser, F. Lazeyras, J. Delavelle and S. Eliez (2006). "Abnormal patterns of cortical gyrification in velo-cardio-facial syndrome (deletion 22q11.2): An MRI study." Psychiatry Research: Neuroimaging 146(1): 1-11.

Sun, T. and R. F. Hevner (2014). "Growth and folding of the mammalian cerebral cortex: from molecules to malformations." Nature Reviews Neuroscience 15(4): 217-232.

Tallinen, T. and J. S. Biggins (2015). "Mechanics of invagination and folding: Hybridized instabilities when one soft tissue grows on another." Physical Review E 92(2): 022720.

Tallinen, T., J. S. Biggins and L. Mahadevan (2013). "Surface sulci in squeezed soft solids." Physical Review Letters 110(2): 024302.

Tallinen, T., J. Y. Chung, J. S. Biggins and L. Mahadevan (2014). "Gyrification from constrained cortical expansion." Proceedings of the National Academy of Sciences 111(35): 12667-12672.

Tallinen, T., J. Y. Chung, F. Rousseau, N. Girard, J. Lefèvre and L. Mahadevan (2016). "On the growth and form of cortical convolutions." Nature Physics 12(6): 588-593.

Tortori-Donati, P., A. Rossi and R. Biancheri (2005). Brain malformations. Pediatric Neuroradiology, Springer: 71-198.
Tuo Zhang, X. L., Xi Jiang, Fangfei Ge, Shu Zhang, Lin Zhao, Huan Liu, Ying Huang, Xianqiao Wang, Jian Yang, Lei Guo, Xiaoping Hu, Tianming Liu (2019). "Cortical 3-hinges Could Serve as Hubs in Cortico-cortical Connective Network." Brain Imaging and Behavior in press.

Van Essen, D. C., D. Dierker, A. Snyder, M. E. Raichle, A. L. Reiss and J. Korenberg (2006). "Symmetry of cortical folding abnormalities in Williams syndrome revealed by surface-based analyses." The Journal of Neuroscience 26(20): 5470-5483.

Van Essen, D. C., H. A. Drury, S. Joshi and M. I. Miller (1998). "Functional and structural mapping of human cerebral cortex: solutions are in the surfaces." Proceedings of the National Academy of Sciences 95(3): 788-795.

Wang, Q. and X. Zhao (2015). "A three-dimensional phase diagram of growth-induced surface instabilities." Scientific Reports 5(1): 8887.

White, T., N. C. Andreasen, P. Nopoulos and V. Magnotta (2003). "Gyrification abnormalities in childhood-and adolescent-onset schizophrenia." Biological Psychiatry 54(4): 418-426.

Wisco, J. J., G. Kuperberg, D. Manoach, B. T. Quinn, E. Busa, B. Fischl, S. Heckers and A. G. Sorensen (2007). "Abnormal cortical folding patterns within Broca's area in schizophrenia: evidence from structural MRI." Schizophrenia Research 94(1): 317-327.

Xintao, H., G. Lei, Z. Tuo, L. Gang, N. Jingxin, J. Xi, Z. Degang and L. Tianming (2010). Joint analysis of fiber shape and cortical folding patterns. Biomedical Imaging: From Nano to Macro, 2010 IEEE International Symposium on.

Xu, G., A. K. Knutsen, K. Dikranian, C. D. Kroenke, P. V. Bayly and L. A. Taber (2010). "Axons pull on the brain, but tension does not drive cortical folding." Journal of Biomechanical Engineering 132(7): 071013.

Yeh, F., V. J. Wedeen and W. I. Tseng (2010). "Generalized $q$-Sampling Imaging." IEEE Transactions on Medical Imaging 29(9): 1626-1635.

Yeh, F.-C., T. D. Verstynen, Y. Wang, J. C. Fernández-Miranda and W.-Y. I. Tseng (2013). "Deterministic Diffusion Fiber Tracking Improved by Quantitative Anisotropy." PLOS ONE 8(11): e80713.
Yu, X., H. Chen, T. Zhang, X. Hu, L. Guo and T. Liu (2013). Joint analysis of gyral folding and fiber shape patterns. Biomedical Imaging (ISBI), 2013 IEEE 10th International Symposium on, IEEE.

Zang, J., X. Zhao, Y. Cao and J. W. Hutchinson (2012). "Localized ridge wrinkling of stiff films on compliant substrates." Journal of the Mechanics and Physics of Solids 60(7): 1265-1279.

Zhang, T., H. Chen, M. J. Razavi, Y. Li, F. Ge, L. Guo, X. Wang and T. Liu (2018). "Exploring 3-hinge gyral folding patterns among HCP Q3 868 human subjects." Human Brain Mapping 39(10): 4134-4149.

Zhang, T., M. J. Razavi, H. Chen, Y. Li, X. Li, L. Li, L. Guo, X. Hu, T. Liu and X. Wang (2017). "Mechanisms of circumferential gyral convolution in primate brains," Journal of Computational Neuroscience 42(3): 217-229.

Zhang, T., M. J. Razavi, X. Li, H. Chen, T. Liu and X. Wang (2016). "Mechanism of Consistent Gyrus Formation: an Experimental and Computational Study," Scientific Reports 6(37272).

Zhang, X., E. Yacoub and X. Hu (2001). "New strategy for reconstructing partial-Fourier imaging data in functional MRI." Magn Reson Med 46(5): 1045-1048.

Zhang, Z., Z. Hou, X. Lin, G. Teng, H. Meng, F. Zang, F. Fang and S. Liu (2013). "Development of the Fetal Cerebral Cortex in the Second Trimester: Assessment with 7T Postmortem MR Imaging." American Journal of Neuroradiology 34(7): 1462-1467.

Zilles, K., N. Palomero-Gallagher and K. Amunts (2013). "Development of cortical folding during evolution and ontogeny." Trends in Neurosciences 36(5): 275-284.
Tables

Table 1. Structural session imaging parameters in HCP 868 dataset.

| Type | Description       | TR(ms) | TE(ms) | Flip Angle | FOV (mm) | Voxel Size                  | Acquisition Time(min:sec) |
|------|-------------------|--------|--------|------------|----------|-----------------------------|---------------------------|
| T1w  | 3D MPRAGE        | 2400   | 2.14   | 8 deg      | 224×224  | 0.7 mm isotropic            | 7:40                      |
| T2w  | 3D T2-SPACE      | 3200   | 565    | variable   | 224×224  | 0.7 mm isotropic            | 8:24                      |

Figure Captions
Figure 1. (a) An illustration to show the concepts of hinge points, hinge lines (dotted lines), and gyrus crest. (b) Example illustrations for 2-hinge, 3-hinge, and 4-hinge patterns.

Figure 2. A piece of brain selected to construct finite element model.
Figure 3. Pipelines of the extraction of the gyral skeleton and 3-hinge patterns. (a) Cortical surface of the white matter/gray matter boundaries. (b)-(d) Gyral crest segmentation and skeletonization on an enlarged region. (b) Presentation of gyral altitudes. Red regions have positive altitude values while blue regions have negative altitude values. (c) The cortical surface is segmented into gyral crests (black dots). (d) Gyral crest skeleton extraction (black curves). (e) The gyral crest skeleton on a brain. (f) The presentation of 3-hinge patterns centers (red dots).

Figure 4. Process of 3-hinge patterns detection. (a) Initial state of the meshed area created by triangular mesh. (b) The deformed coordinates of the cortical surface in Abaqus are reconstructed in MATLAB. (c) The constructed surface is visualized by Paraview software. (d) A developed algorithm detects path lines and center points of 3-hinge patterns. Blue to red shows a transition from convex curvature to concave curvature.
Figure 5. Morphological evolution of a growing brain model. (a) Initial perturbation before simulation. (b) Instability initiation. (c) Folding after instability. (d) Formation of convoluted patterns and 3-hinge patterns. (e) Top view of the highly convoluted cortex. Some 3-hinge patterns are detected on the surface. Red points show centers of 3-hinge patterns and green curves show their patterns.

(a)

(b)

(c)

(d)

(e)
Figure 6. (a) Dependency of numbers of 3-hinge patterns on small initial perturbation. (b) Normal distribution of the number of 3-hinge patterns. (c) An example case to show how the developed algorithm automatically detects the locations of 3-hinge patterns. (d) Variation in location of 3-hinge patterns on the pre-central gyrus (PrCG) and post-central gyrus (PoCG) for four randomly selected subjects. The cortical surfaces of four subjects have been aligned to the gray-ordinate standard system by the HCP preprocessing pipeline (corresponding vertices are of the same ID). We manually identified three 3-hinge patterns on subject #1. The hinge centers are represented by color bubbles. The hinge spokes are represented by solid curves. The anatomical corresponding vertices on subjects #2-#4 via HCP preprocessing pipeline are highlighted by the corresponding color bubbles and black arrows. We also manually identified the corresponding 3-hinges on subjects #2-#4, the centers and spokes of which are represented by dashed circles and curves and color-coded by the correspondences. This Figure has been reused with permission from Ref. (Zhang, Chen et al. 2018).
Figure 7. (a) Dominant shapes of 3-hinge patterns in real brains and FE models. The top numbers (red color) and bottom numbers (blue color) are the percentages found in real brains and FE models, respectively. (b) Comparison of convolution patterns between our FE models (left) and experimental images of real brains (right). In the experimental images, gray matter has been removed for easier analysis of gyral crests.

Figure 8. (a) Fiber density in the 3-hinge patterns are higher than other locations of a brain (red color regions). The reconstructed surface is white matter surface. (b) The cross-section shows how dense fibers are projected to a 3-hinge fold. Black arrow heads in (a) & (b) highlight the same 3-hinge fold. Diffusion MRI of this subject was used to produce the streamline fibers (color curves in (b)) and the white matter surface and the fiber density map on this surface in (a). More details are referred to section ‘Experimental Methods’.
Figure 9. Top view of four FE models with same mechanical and geometrical parameters and different initial perturbations. Locations and 3-hinges patterns are unpredictable.

Figure 10. (a) and (c) Two selected 3-hinge patterns taken from images of a real brain are incorporated into the FE models. (b) and (d) The top view of FE models in initial state and without growth, with highlighted areas containing fibers. (e) and (g) Four FE models with growing fibers along the selected 3-hinge patterns shown in (b) and (d). All parameters of models are same except initial perturbations. After convolution, 3-hinge patterns same as those seen in a real brain form in the center of cortex. (f) and (h) 3-hinge patterns (white lines) are detected by the developed algorithm.
Figure 11. (a) Dependence of number of 3-hinge patterns on the axis ratio of brains between different species. The number of 3-hinge patterns is only for a hemisphere. (b) Dependence of folding patterns and number of 3-hinge patterns on cortical thickness. In FE models, square patches show representative folding patterns of human, chimpanzee, and macaque brains. Size of the patches are selected to be representative of folding patterns.
Figure 12. (a) Dependency of number of 3-hinge patterns to the surface area and initial thickness of cortex. Numbers on the series legends show the areal dimensions of the cortex in centimeters. (b) Dependency of density of 3-hinge patterns in a unit area of models; $N$ is the number of 3-hinge patterns per unit area and $t$ is the initial thickness of cortex.