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Differential Tangential Expansion as a Mechanism for Cortical Gyrification

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Gyrification, the developmental buckling of the cortex, is not a random process—the forces that mediate expansion do so in such a way as to generate consistent patterns of folds across individuals and even species. Although the origin of these forces is unknown, some theories have suggested that they may be related to external cortical factors such as axonal tension. Here, we investigate an alternative hypothesis, namely, whether the differential tangential expansion of the cortex alone can account for the degree and pattern-specificity of gyrification. Using intrinsic curvature as a measure of differential expansion, we initially explored whether this parameter and the local gyrification index (used to quantify the degree of gyrification) varied in a regional-specific pattern across the cortical surface in a manner that was replicable across independent datasets of neurotypicals. Having confirmed this consistency, we further demonstrated that within each dataset, the degree of intrinsic curvature of the cortex was predictive of the degree of cortical folding at a global and regional level. We conclude that differential expansion is a plausible primary mechanism for gyrification, and propose that this perspective offers a compelling mechanistic account of the co-localization of cytoarchitecture and cortical folds.

Keywords: cortical development, differential expansion, gyrification, intrinsic curvature

Introduction

Gyrification, the characteristic folding of the cortical mantle that emerges during development, mitigates the problems inherent in enclosing a large surface area in a small volume. It is thought to be a mechanical process, whereby as yet unknown forces cause the surface to buckle. Any cogent theory of gyrification must account for the fact that, although the consequences of these forces appears to be highly variable across individuals, giving rise to individual-specific variations in the shape, orientation, frequency, and even the presence or absence of gyri and sulci, there is, nonetheless, a surprising level of consistency across individuals. This is especially so for the primary sulci, which are deepest, emerge earliest in prenatal brain development, and are most consistent across individuals. In other words, there is a degree of consistency which suggests that buckling and fissuration are not random but rather are subject to additional constraints.

Although many theories of gyrification have been proposed, direct evidence supporting any 1 theory is lacking. One influential view is that axonal tension between cortical regions induces folding by pulling on the cortex, drawing together regions that are strongly connected, while less-strongly connected regions drift (Van Essen 1997; Mota and Herculano-Houzel 2012). However, there is evidence against this hypothesis. First, axons do not follow the pattern specified by the model—specifically they run parallel to the sulcal walls rather than perpendicular to them (Xu et al. 2010). Second, it has been shown that while axons pull on the brain, they are not under sufficient tension to affect folding patterns of individual gyri, as the primary forces occur in the deep subcortical white matter (Xu et al. 2010). Moreover, cortico-cortical projections as postulated by the model post-date the emergence of the primary sulci, ruling them out as a mechanical factor in gyrogenesis (Goldman-Rakic 1987).

What other processes perhaps internal to the cortex might drive folding? A number of theories have been proposed. These are largely variations on the theme that the tangential expansion of the cortex itself drives folding. One such theory is that the expansion of the cortex is non-uniform in the radial direction, meaning that upper cortical layers expand more than lower layers (Richman et al. 1975). This excess growth in turn is postulated to engender the buckling of the cortex, with varying patterns of differential growth producing the characteristic patterns of gyri and sulci. However, it has been pointed out (Van Essen 1997; Toro and Burnod 2005) that the same pattern of differential growth could equally be a consequence, rather than a cause, of folding. A subsequent modified version of this idea (Toro and Burnod 2005; Xu et al. 2010) suggests that cortical folding arises more simply from tangential surface expansion. According to this view, tangential expansion of the cortex would lead to increases in tangential pressure across the expanding surface with the emergence of folds occurring as a consequence of this pressure and acting to reduce it. Indeed, this expansion model of gyrification is an old idea dating back to the earliest theorists (His 1875; Retzius 1891), and has been a feature of most gyrification theories over the past century (Le Gros Clark 1945; Richman et al. 1975; Todd 1986), with various modifications (for review, see White et al. 2010; White and Hilgetag 2011). However, this explanation alone would predict a relatively random process that cannot account for the consistency of patterns observed across individuals. Such consistency clearly has a genetic component, as shown by studies in monozygotic and dizygotic twins (Bartley et al. 1997; Lohmann et al. 1999).

The failure of these tangential expansion models to account for pattern-specific folding, and thus for the genetic contribution to gyrification may be overcome by considering the consequences of a differential, rather than a uniform cortical expansion. If the cortex were to expand differentially in a

predictable pattern, it would in turn give rise to predictable stress lines across the surface in the manner of a folded sheet of paper repeatedly bending at a predefined crease. In turn, these predictable stress lines would inevitably lead to consistent patterns of folding.

In support of this, there is considerable evidence that the cortex does indeed differentially expand. At the most basic level, there is a non-uniform spacing between cells throughout the cortex, while at another scale, different cytoarchitectural regions have different degrees of horizontal spacing between neurons (Semendeferi et al. 2011). Indeed, it has been demonstrated that cortical progenitor cells are differentially distributed across the cortex and co-localize with regions of the greatest tangential expansion (Reillo et al. 2011). Finally, there is a rostral-caudal gradient to cortical development at the earliest stages (Smart et al. 2002). Thus, the differential mechanical properties arising from region-specific development and/or cortical architecture may mediate cortical expansion in a non-random manner. According to this model of cortical folding, the pattern specificity of gyrification across individuals is dependent on the cytoarchitectural patterning and development of the cortex, for which there is considerable evidence. In this way, the differential expansion of the cortex can account for the pattern specificity of cortical folds. Additionally, this model of gyrification may account for not only the genetic component of gyrification, but also the high degree of correspondence observed between cytoarchitecture and gyrification patterns (Welker 1990; Fischl et al. 2007), whereby folds may occur along predictable lines of stress arising from differential expansion between areas.

In summary, regional variations in expansion due to development, cytoarchitecture or both, may give rise to a characteristic differential tangential expansion of the cortex, which in turn may induce pattern-specific gyrification. In order to investigate this hypothesis, it is necessary to quantify both the degree of differential tangential expansion, as well as its pattern-specificity across the cortex, and compare these to the corresponding regional degree and pattern of gyrification.

Traditionally, gyrification has been quantified as the ratio of the total cortical surface to a reference surface, with larger ratios implying greater degrees of folding (Zilles et al. 1988; Schaer et al. 2008). Depending on how it is quantified, the degree of gyrification can be somewhat ambiguous in that it cannot differentiate between a surface with few deep folds, as opposed to one with many shallow ones. However, when quantified at a suitable scale (Schaer et al. 2008), and at a regional level, it is easier to distinguish between these possibilities. Thus, the so-called local Gyrification Index (lGI) (Schaer et al. 2008) may be reasonably adopted as a suitable parameter of the gyrification pattern, sensitive to the differences in the degree of folding that arise from different folding shapes.

We therefore used lGI to quantify gyrification. In order to relate this to the degree of differential tangential expansion of the cortex, we used intrinsic curvature as a marker of the latter (Todd 1985; Ronan et al. 2011). Intrinsic curvature is a mathematically fundamental property of a surface, and arises out of differential growth—if one region expands faster than another (a differential), the surface will curve. There are 2 ways in which this can happen: if the center of a patch expands faster than the edges, then it will produce a bump, analogous to a hemisphere. This is called positive curvature. If the edges expand faster than the center, it will produce a wavy, saddle-like shape. This is called negative curvature. The degree of this curvature is dependent on the degree of the differential, with a bigger differential resulting in a greater degree of curvature. In this way, we can use measures of cortical intrinsic curvature as a marker for the differential expansion of the surface. The intrinsic curvature of the cortex has been studied previously, and is demonstrated to have a spatial frequency greater than that of gyri and sulci (Pienaar et al. 2008; Ronan et al. 2011), when quantified at a millimeter scale (see Fig. 1). Indeed, it may provide a more sensitive measure of neurodevelopmental anomalies than larger scale gyrification measures (Ronan et al. 2012).

In summary, we argue that intrinsic curvature, which is readily measurable on high-resolution cortical reconstructions, informs us about the interplay between surface expansion and region-specific factors that induce a differential. Given this, we propose that it is a suitable parameter to test the hypothesis that regional differential expansion is predictive of regional gyrification. Observation that this small-scale measure correlated with gyrification measures would provide a powerful piece of evidence in favor of this view.

Explaining pattern-specific folding is a key challenge for any gyrification theory. For this reason we tested whether regional differences in the degree of gyrification were reflected in regional differences in the degree of intrinsic curvature, and further whether these patterns were consistent across datasets. Finally, to test the differential expansion model of gyrification, we assessed the relationship between cortical intrinsic curvature and lGI both a global and a regional scale.

Materials and Methods

Subjects and MR Image Data

To demonstrate the robustness and replicability of pattern-specific gyrification and intrinsic curvature across the cortex we analyzed 2 independent datasets.

Group 1

Sixty-five controls (19.1 ± 5.3 years, males 34; females 31) were recruited as part of an ongoing longitudinal brain imaging/genetics study conducted at the Child Psychiatry Branch of the National Institute of Mental Health (Giedd et al. 1999). All scans were obtained using the same 1.5-Tesla GE Signa scanner at the NIH Clinical Center in Bethesda, MD, USA. Whole-brain T_1-weighted images were acquired using a 3D spoiled gradient-recalled pulse sequence with the following parameters: axial orientation; image matrix 256 × 192; in-plane resolution of 0.9375 by 0.9375 mm; 124 slices of slice thickness 1.5 mm, TE = 5 ms; TR = 24 ms; flip angle = 45°.

Group 2

Fifty-nine controls (26.7 ± 9.4 years, males 37; females 22) were recruited with the guidance of the Oxford and Berkshire Psychiatric Research Ethics Committees, UK. Written informed consent was obtained from all participants (and their parents if under the age of 16). Structural MRI data were acquired using a 1.5-T Sonata MR imager (Siemens, Erlangen, Germany) with a standard quadrature head coil and maximum 40 mT m^{-1} gradient capability at the Oxford Centre for Clinical Magnetic Resonance Research. Whole-brain T_1-weighted images were acquired with a FLASH sequence using the following parameters: coronal orientation, image matrix = 256 × 256, with 1 × 1 mm^2 in-plane resolution, 208 slices of slice thickness 1 mm, TE = 5.6 ms, TR = 12 ms, flip angle $\alpha = 19^{\circ}$.

Cortical Reconstruction and Analysis

Cortical reconstructions were generated using the software *FreeSurfer* (Dale et al. 1999; Fischl, Sereno and Dale 1999a; Fischl, Sereno and

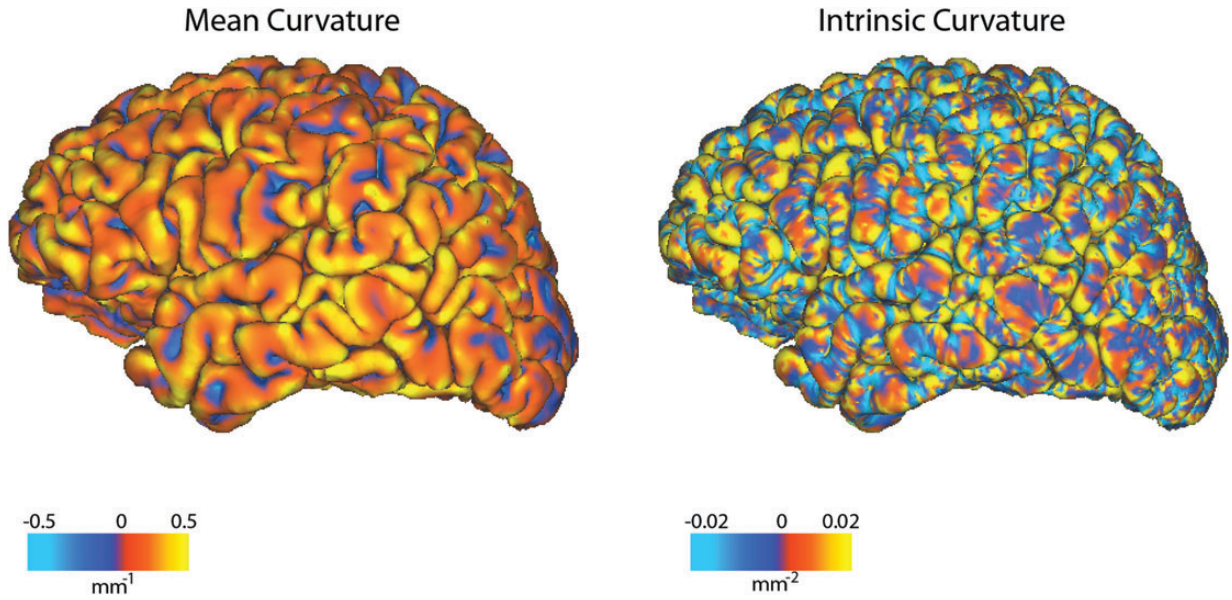

Figure 1. The mean and intrinsic curvature of the cerebral cortex quantified at a millimeter scale. Mean curvature reflects the extrinsic folds of sulci and gyri; however, the intrinsic curvature is of a much higher spatial frequency.

Tootell et al. 1999b; Fischl and Dale 2000). The *FreeSurfer* program was specifically developed for cortical reconstruction. In brief, raw image data voxels were subsampled to voxels of side 1 mm^3. After that the data were normalized for intensity. RF-bias field inhomogenieties were modeled and removed, followed by skull-stripping. The cerebral white matter was subsequently identified after which the hemispheres were separated, tessellated, and deformed to produce an accurate and smooth representation of the gray-white interface. In case of inaccuracies, the reconstructions were edited by hand. These edits were made on 2D slices though the reconstruction and hence may be considered to be effectively unbiased with respect to the morphological parameters which are three dimensional.

Intrinsic Curvature

The software Caret (v5.65, http://brainmap.wustl.edu/caret) was used to calculate cortical intrinsic curvature per vertex of each subjects' FreeSurfer-reconstruction. In brief, for each individual the reconstruction of the pial surface was imported in to Caret prior to curvature calculation. There are several different ways to calculate the intrinsic curvature of a surface (do Carmo 1976), however because meshed surfaces are not differentiable, alternative approximation methods have been developed (Surazhsky et al. 2003). In the CARET software, curvature estimations are based on the local curvature matrix. This matrix, also known as the Hessian or second fundamental form of the surface, can be considered to capture the rate of change of the surface normal which in turn is a measure of the curvature of the surface.

$$H = \begin{pmatrix} L_{xx} & L_{xy} \\ L_{xy} & L_{y} \end{pmatrix} \quad (1)$$

where L_{xx} indicates the second derivative of the surface normal.

In CARET, the surface normal per vertex is taken as the average of the normal for each tile containing the vertex (Drury et al. 1996) (see Fig. 2). The curvature matrix is solved using a method of least squares to produce the eigenvalues which are the principle curvatures (Maillot et al. 1993). By definition, intrinsic curvature is the product of the principle curvatures.

When quantified at the millimeter-scale cortical intrinsic curvature has a high spatial frequency pattern alternating between positive and negative intrinsic curvature. This is akin to the geometric necessity of having an outward-fold between 2 inward folds. In order to maximize the power of our intrinsic curvature measures, we included both positive and negative intrinsic curvature values in our experiments by calculating the modulus intrinsic curvature for each subject. To do this, we isolated the negative intrinsic curvature values of each subject's cortical mesh, took the modulus of these negative values, and recombined them to the positive curvature values to make a positive distribution which reflected both positive and negative intrinsic curvature values. The derived surface curvature files were subsequently imported to MatLab where a low-pass filter was applied. The purpose of filtering was to remove aberrantly high curvature values that were not compatible with the resolution of the cortical reconstruction. Further details on this process are included elsewhere (Ronan et al. 2011, 2012).

Local Gyrification Index

Gyrification was assessed using a 3D measure called the lGI (Schaer et al. 2008). The lGI is a ratio of the total cortical surface area to a reference surface, with higher indices implying a greater degree of gyrification. The lGI is calculated as the ratio of surface areas between a patch of cortical area that follows the folding of the cortex, and the area of a reference surface that encloses the patch. This is calculated per vertex of the cortical reconstruction for a patch of 25 mm, generating a centimeter-scale measure of the local folding of the cortex. Further details of these methods are available in Schaer et al. (2008).

Analysis

Intrinsic Curvature Skew

As discussed above, we postulate that intrinsic curvature may be adopted as a morphological parameter of differential expansion. As the rate of differential expansion increases, the degree of intrinsic curvature increases, with greater rates producing proportionately more extreme curvature values. However, the differential component of the growth also implies that the shape of the distribution will change, with proportionately fewer extreme curvature values produced as the rate of differential growth increases (Ronan et al. 2011). Thus, the shape of the distribution will change (due to the differential component of expansion) as well as the relative position of its average (due to overall increase in size). For this reason, we quantified the skew of the positive intrinsic curvature distribution per subject, rather than its average as a less ambiguous parameter of the differential aspect of expansion (Ronan et al. 2012). Previous studies of cortical

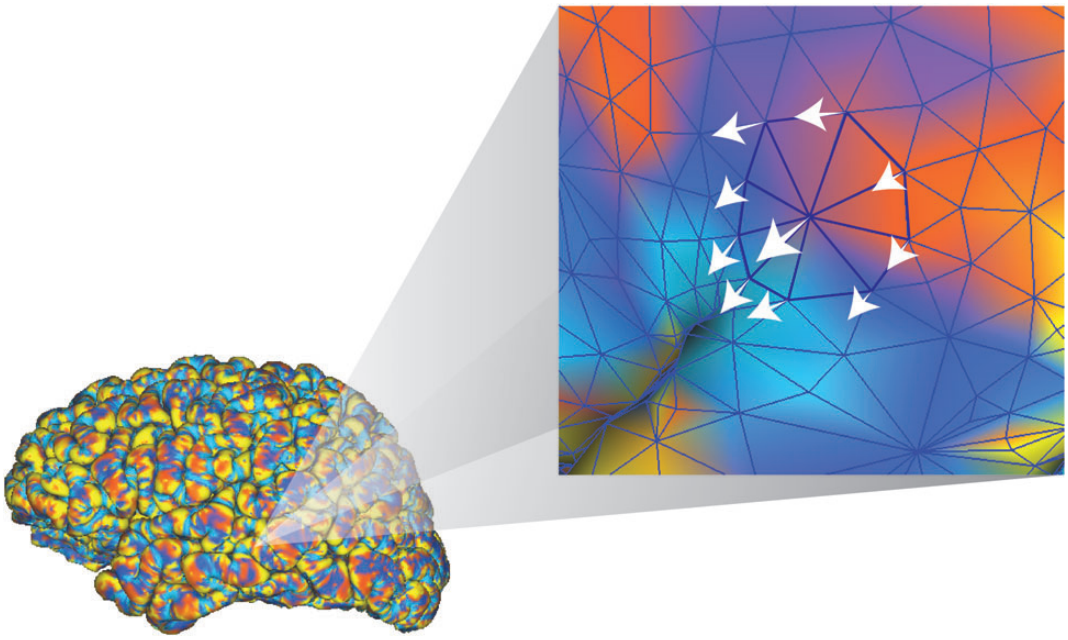

Figure 2. Illustration of Caret-derived intrinsic curvature which is calculated per vertex on the FreeSurfer-derived surface reconstruction. In the vertex illustrated, the associated surface normals are drawn. For the calculation of curvature at this vertex, the surface normal is taken as an average of these surrounding surface normals.

intrinsic curvature have demonstrated that the distribution of intrinsic curvature, like other measures of biological morphology (Winkler et al. 2012), is non-normally distributed (Pienaar et al. 2008; Ronan et al. 2011). Thus, more extreme skew indicates a distribution more heavily weighted towards zero curvature, which in turn is interpreted as relatively less differential growth.

Regional Analysis

A key challenge for gyrification theory is to account for the factors that mediate cortical expansion to produce pattern-specific folding. Thus, as an initial test of the hypothesis that gyrification is driven by differential expansion, we sought to establish whether cortical intrinsic curvature, as well as lGI, varied in a characteristic way across regions of the brain.

We initially explored this by dividing the cortex into 2 regions of interest, namely, a region of high and low lGI. To do this, we used the normal distribution of lGI values, which are typically increased in the area around the insula (Schaer et al. 2008). To delineate a boarder between low and high lGI regions, we masked the cortical surface at an arbitrary threshold of lGI = 3.5 in a single subject to make a mask of "lGIMax"; all other cortical regions were subsequently labeled "lGIMin" (see Fig. 3). These masks were then mapped to all other subjects in the same dataset.

We subsequently carried out a more detailed analysis of the pattern of lGI and intrinsic curvature by dividing each individuals cortical reconstruction into the 6 lobes of the brain (cingulate, frontal, insula, parietal, occipital, and temporal), which were defined using the Desikan-Killiany atlas (Desikan et al. 2006) which is part of the *FreeSurfer* 5.1 distribution.

Statistical Analysis

All data were tested for normality prior to analysis, and corrected where necessary using the BoxCox transform. The linear regression of gyrification (lGI) was quantified globally and regionally using a linear mixed-effects model with fixed effects of intrinsic curvature, hemisphere, age, and sex. Random effects of group and individual were also modeled. Statistical analysis was conducted in R using the "lme4" and "languageR" packages (Baayen, Davidson, and Bates 2008).

Results

Regional Variations in lGI, Intrinsic Curvature

Data were divided in to regions of low lGI (<3.5) and high lGI (>3.5). For each dataset, we plotted the mean and standard error of lGI and cortical intrinsic curvature skew (Fig. 3). For both datasets, there was a significant difference in the mean intrinsic curvature skew per region, with regions of high lGI demonstrating more skew than the rest of the cortex (group 1 intrinsic curvature $F_{1,192} = 81$, $P < 0.0001$; group 2 intrinsic curvature $F_{1,174} = 99$, $P < 0.0001$).

When the data were divided in terms of lobes, the results of ANOVA indicated a significant lobe difference in each parameter for each dataset (group 1 lGI $F_{5,\ 704} = 2603$, $P < 0.0001$; intrinsic curvature $F_{5,704} = 311$, $P < 0.0001$; group 2 lGI $F_{5,638} = 171$, $P < 0.0001$; intrinsic curvature $F_{5,638} = 297$, $P < 0.0001$). Once again, plots of mean values demonstrated patterns of lGI and intrinsic curvature that were consistent across datasets (Fig. 3).

lGI versus Intrinsic Curvature: Global

For each dataset at the global (whole-brain) level, the degree of local gyrification was significantly predicted by the degree of intrinsic curvature (group 1 $t = -3.1$, $P = 0.003$; group 2 $t = -4.4$, $P = 0.0001$). There was no significant curvature-by-hemisphere effect in either group. For both groups, an increase in the degree of intrinsic curvature (decreasing curvature skew) was correlated with an increase in the degree of folding. Results are illustrated in Figure 4.

lGI versus Intrinsic Curvature: lGI Max versus lGI Min

When we combined the datasets and looked at the regions (lGIMax, lGIMin) individually with "group" and "subject" as random effects, intrinsic curvature was a significant predictor of gyrification in each region (lGIMax $t = -3.7$, $P = 0.0002$;

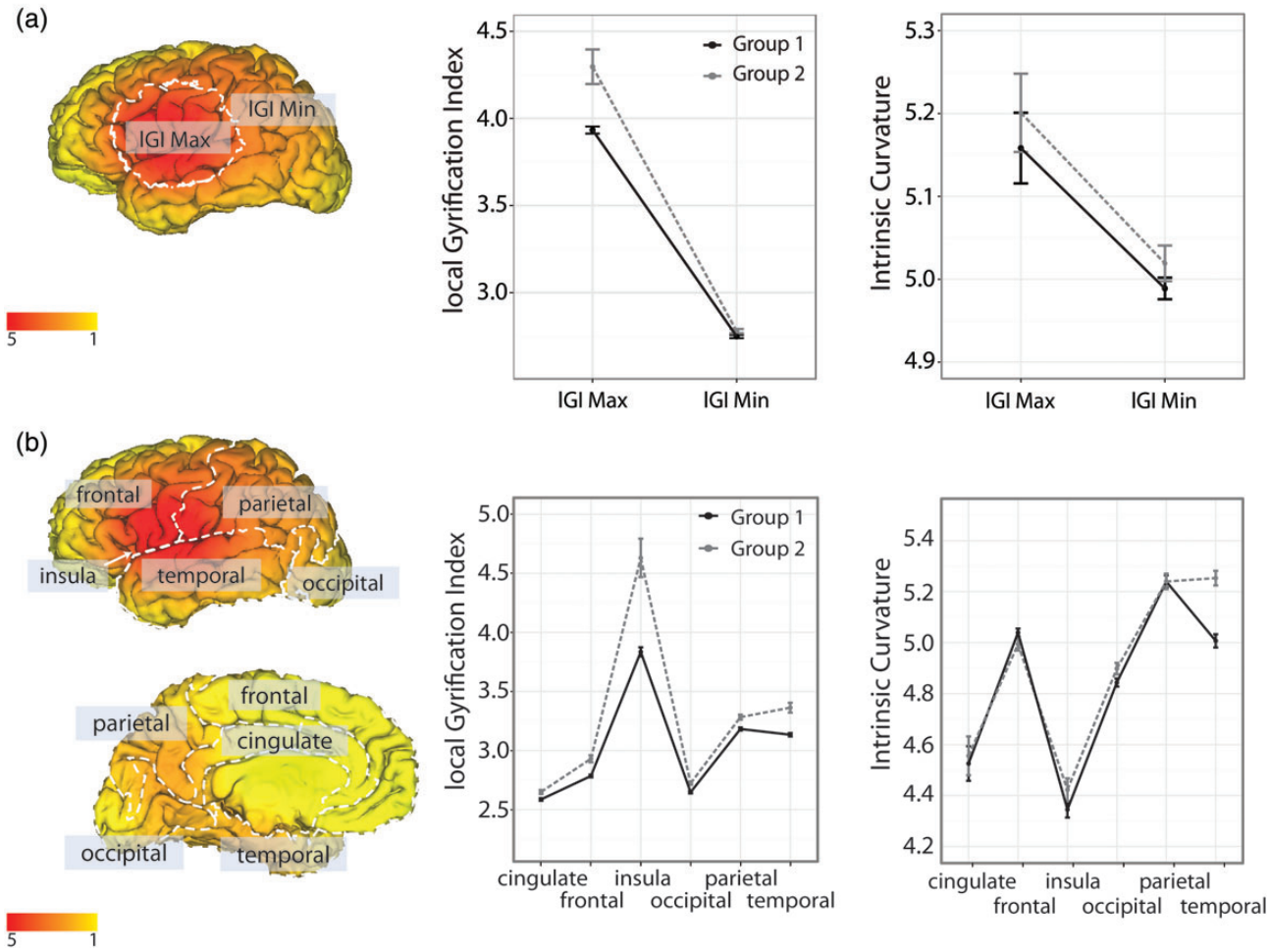

Figure 3. (*a*) The natural variation of IGI was used to delineate regions of "high" IGI (>3.5) and "low" IGI (<3.5). Line plots of mean and standard error indication that for each dataset, the intrinsic curvature demonstrated a similar variation between regions of high and low IGI. (*b*) Line plots of mean and standard error for. IGI and intrinsic curvature across 6 cortical lobes indicate a consistent pattern across datasets for each parameter.

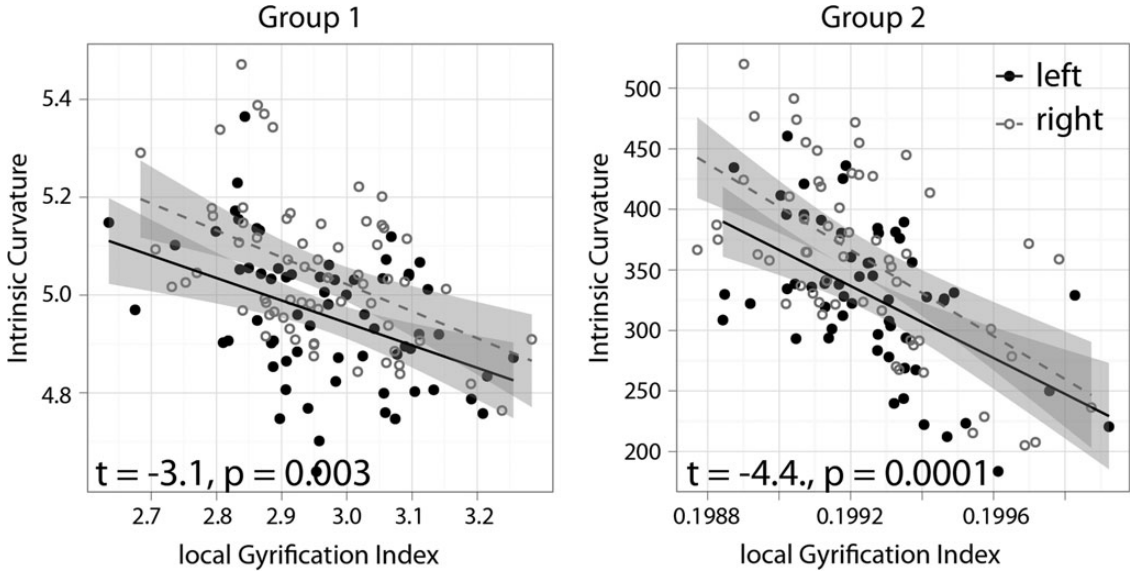

Figure 4. Scatter plots of intrinsic curvature and IGI values per hemisphere for each independent dataset.

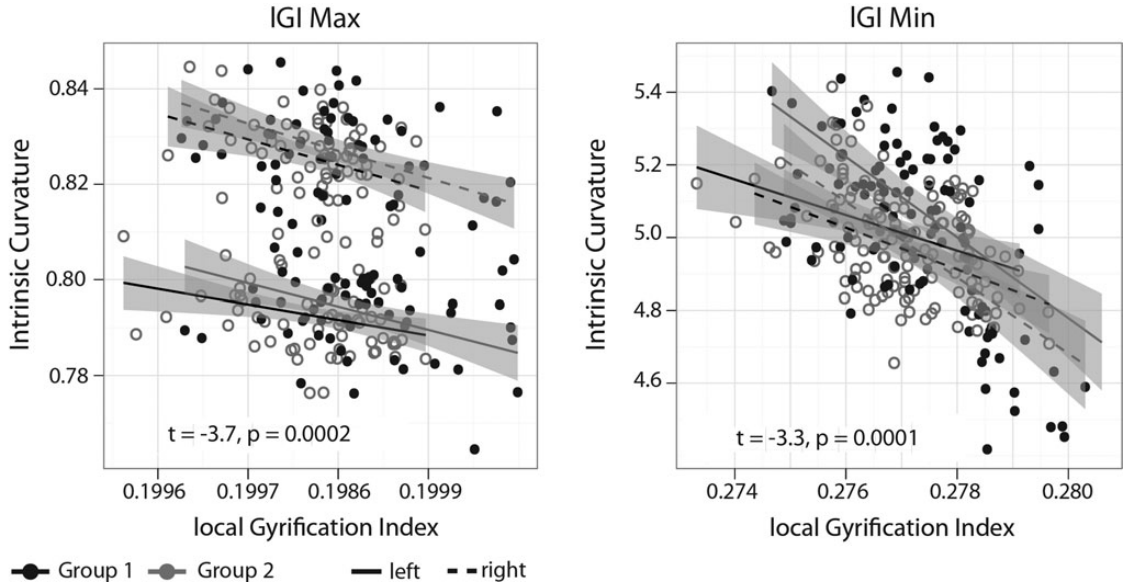

Figure 5. Scatter plots of intrinsic curvature and lGI values per hemisphere per region (high lGI vs. low lGI) for each independent dataset.

lGIMin $t = -3.3$, $P = 0.0001$). There were no significant effects of group, or curvature-by-group interactions. Once again, an increase in the degree of intrinsic curvature (decreasing skew) was correlated with an increase in the degree of folding (Fig. 5).

lGI versus Intrinsic Curvature: Lobes

When we treated the lobes as individual regions with "group" and "subject" as random effects, intrinsic curvature was a significant predictor of the degree of gyrification in each region (cingulate $t = 4.3$, $P = 0.02$; frontal lobe $t = -4.4$, $P = 0.0001$; insula $t = -2.8$, $P = 0.004$; occipital lobe $t = -4$, $P = 0.0001$; parietal lobe $t = -3.1$, $P = 0.001$; temporal lobe $t = -10.9$, $P = 0.0001$). In all but one of the lobes, there was a negative correlation between intrinsic curvature skew and lGI in agreement with theory (Fig. 6).

Discussion

The aim of this study was to test the differential expansion hypothesis of cortical gyrification which postulates that regional differences in tangential cortical expansion are a primary driver of gyrification. Moreover, given that these differences may arise due to differences in cytoarchitecture or developmental rates, this link can account for the relative consistency of folding patterns observed within, and, to an extent, across species. To test this theory, we used millimeter-scale cortical intrinsic curvature as a morphological parameter of differential expansion, and related this parameter to the degree of folding of the cortex. We additionally demonstrated that, like gyrification, intrinsic curvature has a regional specificity, which is consistent across datasets. Overall, the results of this study support previous theoretical models (Toro and Burnod 2005; Nie et al. 2010; Xu et al. 2010) which suggest that the mechanical pressure of the expanding cortical surface is the primary force which drives folding, and further that relative differences in cortical architecture or regional development might mediate this expansion in a characteristic way, giving rise to the familiar folding patterns observed.

Although the differential expansion model of gyrification dates back to the earliest theorists, more contemporary views of gyrification have proposed that axonal tension causes and directs the formation of cortical folding (Van Essen 1997; Hilgetag and Barabas 2005). While the axonal-tension theory provides a description of how gyrification arises, the evidence that it is incorrect, as previously discussed, is convincing. Because of this, the differential hypothesis of gyrification has been revisited, albeit indirectly through computational models (Toro and Burnod 2005; Nie et al. 2010; Xu et al. 2010). Most recently, investigations into the spatial and temporal variations of the developing ferret brain indicates support for the hypothesis that folding is commensurate with differential expansion (Knutsen et al. 2013).

The deceptively straightforward correlation of 2 cortical morphological parameters, that is intrinsic curvature and lGI, belies a more fundamental observation, namely, that the distinct mathematical nature of each parameter is critical to the consideration of how they arise. Simply put extrinsic folding alone does not, by definition, change the surface: rather it changes how it is embedded in space. More simply, extrinsic folding does not induce intrinsic curvature. However, changes to intrinsic curvature, either by a non-uniform expansion or surface stretching/compression (both of which are differential by definition) do cause changes to extrinsic folding. That is, if intrinsic curvature changes then extrinsic curvature will also change, but the reverse does not hold true. Thus, the more mathematically fundamental nature of intrinsic curvature supports the hypothesis that cortical gyrification arises from differential tangential expansion of the cortex rather than intrinsic curvature arising as a consequence of extrinsic folding.

Origin of Differential Expansion

The developmental expansion of the cortex is related to the increase in size of cortical cells and the growth of their connections. It has previously been observed that there is a

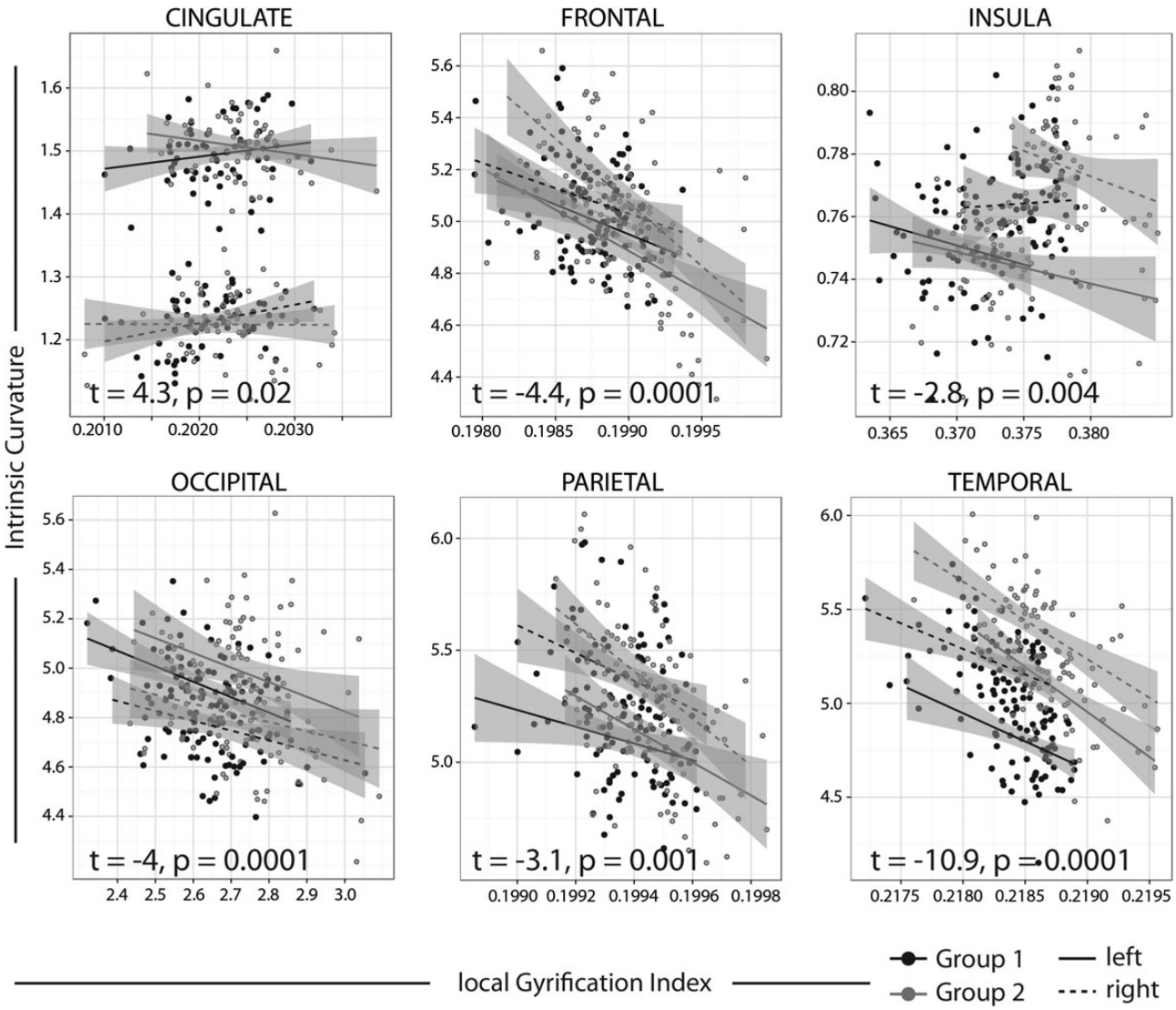

Figure 6. Scatter plots of intrinsic curvature and lGI values per hemisphere per lobe (cingulate, frontal, insula, occipital, parietal, temporal) for each independent dataset.

rostral-caudal gradient in cortical development (Smart et al. 2002) which may in turn induce a similar gradient of differential expansion. At a more regional scale, it may be also that local differences in cytoarchitecture give rise to differing mechanical properties which in turn mediate expansion. We have previously postulated that intrinsic curvature may be sensitive to differences in cytoarchitecture over and above the degree of overall cortical expansion (Ronan et al. 2011, 2012). In brief, we hypothesize that, under expansion, regions with high neuronal density will expand less than regions of lower density due to a comparative increase in tangential pressure which will act to reduce spatial variance between surface components. This in turn results in a more uniform distribution of neurons and hence a lower degree of differential expansion by definition. In this way, it may be that variable cytoarchitecture will result in a differential cortical expansion.

It is also possible that the scale of regional differences may also be manifest at the level of gyri and sulci themselves. Observations of the developmental cortex suggest that early differences in the cytoarchitecture are predictive of the emergence of individual folds (Smart et al. 2002; Bayer and Altman 2006; Kriegstein et al. 2006; Pontious et al. 2008; Lui et al. 2011; Reillo et al. 2011). This has lead to the hypothesis that these changes are specific to gyrencephalic mammals, particularly primates (Fietz et al. 2010). However, there is some controversy over the correlation of these observations with the onset of gyrification (Garcia-Moreno et al. 2012; Hevner and Haydar 2012; Kelava et al. 2012), with similar changes observed in lissencephalic primates and gyrencephalic rodents. What is noticeably consistent however is the relationship between surface expansion and gyrencephaly across species. Because of this, we suggest that gyrification is more appropriately conceived as a function of expansion (and by extension differential expansion), with the same mechanism underpinning the formation of gyri and sulci in all species, rather than a process driven by cell or layer-specific changes in the developing cortex.

How Does the Pattern Specificity of Gyrification Arise?

The pattern specificity of sulcal/gyral folds suggests that gyrification is a directed mechanical process with a characteristic

form of spatial frequency, orientation, depth, and position of folds. The presumption is that patterns are to some extent genetically determined. Heritability studies of twins have supported this theory (Bartley et al. 1997; Lohmann et al. 1999).

Given that we hypothesize that gyrification arises from a differential expansion of the cortex influenced by regional variations in cytoarchitecture, and that relative consistency of gyrification occurs as a consequence of consistency in the pattern of cytoarchitecture, it is worth considering briefly how the latter patterns arise. Recent work has demonstrated that pattern-specific cytoarchitecture is largely a function of genetic control of early development (O'Leary et al. 2007; Chen et al. 2012). Cortical arealization has been demonstrated to be a developmental precursor of gyrification (Kriegstein et al. 2006; Reillo et al. 2011), and disruptions of this have been linked to significant changes in the degree and patterning of cortical gyrification (Richman et al. 1975; Rakic 1988; Piao et al. 2004). These observations support the view that factors governing gyrification reside in the cortex itself.

By definition, this interpretation of pattern formation accounts for another feature of gyrification, namely, the strong correlation between cytoarchitecture and cortical folding (Welker 1990; Fischl et al. 2007). It has been demonstrated that cortical folding is strongly predictive of the boundaries of several Broadmann areas, supporting the hypothesis that specific architecture may produce a predictable mechanical response under expansion to engender buckling.

Finally, given this link between gyrification and differential cortical expansion, we can hypothesize a distinction in the degree of folding across the cortex, whereby primary sulci may reflect regions under a strong and more direct genetic influence in the developing brain (Lohmann et al. 2008), increasing their consistency across individuals, while secondary and tertiary folds may reflect a less-directed mechanical process because they emerge in the context of distortions produced by larger, more stable primary folds and must accommodate these accordingly. Thus, secondary and tertiary folds will be more variable across individuals. In this case, the model of gyrification as tangential expansion moderated by cytoarchitecture may account for the comparatively greater degree of heritability of primary sulci compared with secondary and tertiary sulci. Of course this is speculative, but it nevertheless a plausible explanation for the differing degrees of consistency across primary, secondary, and tertiary folds.

Gyrification and Connectivity

Within the context of the axonal tension theory, axons have been considered to exert a mechanical role in the formation of sulci and gyri. However, while this theory has been called in to question (Xu et al. 2010), axons may yet play a fundamental part in gyrification through their role in early areal specialization of the cortex (Kostovic and Rakic 1984; Rakic 1988), an essential aspect of the development of appropriate cytoarchitecture and hence normal patterns of cytoarchitecture.

More generally, it has long been supposed that the process of gyrification reflects cortical connectivity; however, without a clear understanding of the mechanics, it has been difficult to generate a specific interpretation of the nature or direction of this association. Although the axonal tension theory postulated a direct link between folds and cortical connections, it lacked a directed explanation for other key observations, such as the overall shift in cortical connectivity to proportionately more short-range connections with increasing brain size and hence increasing degrees of gyrification. We have elsewhere speculated on the link between cortical intrinsic curvature and tangential cortico-cortical connectivity, where, by virtue of the implications of differential expansion, we relate an increase in the degree of intrinsic curvature to a shift in the distribution of tangential corticocortical connectivity to favor more short-range connections (Ronan et al. 2011). Such theoretical considerations may reasonably explain the mechanism whereby larger brains with increased degrees of gyrification will naturally favor proportionately more short-range connections.

Conclusion

Gyrencephaly is observed in multiple, independent lineages (Kriegstein et al. 2006) suggesting that a single mechanism related to cortical expansion underlies the development of cortical folding. We have presented here evidence that the mechanical effects of gyrification are predicted by regionally specific differential expansion of the cortex. This evidence supports the hypothesis that the degree and pattern of gyrification is a cortex-specific process, driven by expansion, and mediated by cortical architecture and growth rates.

Cortical shape is necessarily a function of gyrification; however, there is no unique morphological parameter that can adequately describe the various aspects of brain morphometry. For this reason, morphological studies have been rich, but somewhat fragmented, with various parameters capturing different features of the cortex. By understanding the mechanics of how the brain achieves it shape, it is possible to delineate theories which directionally relate morphology to underlying cytoarchitecture and cortico-cortical connectivity. As we have demonstrated here, intrinsic curvature, as well as being mathematically fundamental, is a powerful way to investigate several complementary aspects of the cortex. Additionally, because we can quantify intrinsic curvature at a millimeter scale, it may be more sensitive to subtle changes in the cortex which may otherwise be obfuscated by larger scale measures (Ronan et al. 2012). The ability to measure such subtle changes in cortical morphology may offer improved sensitivity to diagnostically relevant abnormalities, for example, in patients with epilepsy, that can be difficult to localize and delineate based on conventional imaging.

Our findings are compatible with previous assertions that a detailed characterization of the intrinsic geometry of the cortex may offer useful complementary insights in to brain structure and function (Todd 1986; Griffin 1994).

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