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Imaging local genetic influences on cortical folding

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Recent progress in deciphering mechanisms of human brain cortical folding leave unexplained whether spatially patterned genetic influences contribute to this folding. High-resolution in vivo brain MRI can be used to estimate genetic correlations (covariability due to shared genetic factors) in interregional cortical thickness, and biomechanical studies predict an influence of cortical thickness on folding patterns. However, progress has been hampered because shared genetic influences related to folding patterns likely operate at a scale that is much more local (<1 cm) than that addressed in prior imaging studies. Here, we develop methodological approaches to examine local genetic influences on cortical thickness and apply these methods to two large, independent samples. We find that such influences are markedly heterogeneous in strength, and in some cortical areas are notably stronger in specific orientations relative to gyri or sulci. The overall, phenotypic local correlation has a significant basis in shared genetic factors and is highly symmetric between left and right cortical hemispheres. Furthermore, the degree of local cortical folding relates systematically with the strength of local correlations, which tends to be higher in gyral crests and lower in sulcal fundi. The relationship between folding and local correlations is stronger in primary sensorimotor areas and weaker in association areas such as prefrontal cortex, consistent with reduced genetic constraints on the structural topology of association cortex. Collectively, our results suggest that patterned genetic influences on cortical thickness, measurable at the scale of in vivo MRI, may be a causal factor in the development of cortical folding.

Significance

Major gaps remain in our understanding of mechanisms that underlie the folding of the human cerebral cortex. Stereotyped folding in specific cortical locations could be explained by a corresponding anatomical pattern of genetic influences on cortical development, but no direct evidence supports this explanation. Here, we use high-resolution brain MRI to show the existence of the predicted pattern of genetic influences on the thickness of the cerebral cortex, leveraging the prediction that shared genetic influences during development create covariability of cortical thickness in adult neuroanatomy. Anatomically local covariability in cortical thickness has a genetic basis, is symmetric between cortical hemispheres, shows consistency across independent datasets, and may influence patterns of surface folding on the human brain.

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highly penetrant genetic mutations that disrupt both folding and cortical thickness (17).

As comprehensive spatial maps of cytoarchitecture and gene expression from the human cortex during prenatal life do not yet exist, neuroimaging studies have provided a critical source of information about human cortical arealization and its relationship to folding that complements other sources of evidence (18). Analysis of brain MRI data has quantified human variability in sulcal locations; the relationship between morphological phenotypes such as sulcal depth, curvature, and cortical thickness; and the heritability of these and other morphological features (19–22). A putative genetic basis for stereotyped patterns of folding may be reflected in regionally varying genetic influences on morphological features such as thickness that influence folding (4, 23–25). Overlap in interregional genetic influences on thickness can be quantified by the genetic correlation (the shared genetic basis for the phenotypic correlation between two traits), which is likely due to pleiotropy. Indeed, it is known that shared genetic influences account for a great deal of interregional correlations in morphology at the phenotypic level (which has also been called “structural covariance”) (26–30).

Despite this progress, what might be called “local” patterns in phenotypic or genetic correlations—the shared genetic influences on adjacent, small areas of brain and how these vary across the cortex—have not yet been a focus of investigation, significantly limiting the informativeness of prior studies. The paucity of investigations at this resolution is particularly unfortunate because local genetic patterning is likely to be important for folding, a local phenomenon that occurs at an intraregional scale. Shared (or distinct) genetic influences at the centimeter or subcentimeter scale more plausibly influence folding than do long-distance genetic correlations between regions separated by multiple gyri and sulci. If the hypothesized relationship between local genetic influences and folding does exist, then we would expect a neuroanatomical correspondence between maps of local correlation and maps of folding, the latter of which can be quantified by the measurement of curvature (18, 31). Moreover, correlations along the sulcal or gyral axis may have different strengths than correlations that are tangential to these axes in the direction of cortical folding. The present study tests these hypotheses by developing and applying analytic methods to two large in vivo genetically informative neuroimaging datasets totaling over 2,500 scans. Our study discovers profoundly variegated patterns of local genetic correlations in cortical thickness. The spatial patterning of these local genetic correlations is intimately related to sulcal/gyral topology—providing evidence for a patterned genetic influence on cortical folding.

Results

The methodologies developed for this study successfully identified maps of covariability in cortical thickness within local “neighborhoods” of the cerebral cortex (Fig. 1). This covariability was found to have a basis in genetic influences. The strength of these local genetic influences varied markedly across different areas of cortex and was robustly related to cortical folding. These maps of patterned local influences on cortical thickness, identifiable in the adult human brain, may reflect molecular signaling gradients, cellular variation, and laminar features that influence neurodevelopmental cortical folding.

The Genetic Basis of Local Phenotypic Correlations. In theory, the strength of local phenotypic correlations could be homogeneous throughout the cortex, or any heterogeneity could be driven exclusively by nongenetic factors. In order to reject these null hypotheses, we used data from both the Genetics of Brain Structure and Function Study (GOBS) (1,443 individuals) and the Human Connectome Project (HCP) (1,113 individuals) (30, 32–34), processed with FreeSurfer to yield maps of cortical thickness (the distance between the gray–white surface and the pial surface) at ∼10,000 vertices per hemisphere. Spatially varying maps of local correlations in cortical thickness were identified in both of these two large neuroimaging datasets, supporting the conclusion that local phenotypic correlations in cortical thickness were not homogenous throughout the cortex (Fig. 2). Univariate heritability was also reasonably high throughout the cortex (SI Appendix, Fig. S1), indicating that a nontrivial amount of the phenotypic variance was accounted for by genetic factors.

In addition, the pattern of average local phenotypic correlations between neighboring vertices (phenotypic \( L_p \)) recapitulated the pattern of the average local genetic correlation (genetic \( L_p \), isolated based on the extended pedigree structure in the GOBS, which is optimized for genetic analyses). For both phenotypic and genetic correlations, relatively low \( L_p \) occurred in the fundus of the central sulcus, the circular sulcus of the insula, superior and inferior temporal sulci, cingulate sulcus, and the anterior portion of the calcarine sulcus. In contrast, relatively high \( L_p \) was present in the postcentral and precentral gyri, the short insular gyrus, and the superior and middle temporal gyri. \( L_p \) was also moderately high throughout prefrontal cortex (Fig. 2). The observed genetic–phenotypic correspondence was statistically significant (Pearson’s correlation coefficient, \( r = 0.64; P_{\text{spin}} < 0.001 \)) per a randomization procedure (the “spin test”) based on a null model of random alignment of the cortical surface (35). Importantly, the between-sample genetic–phenotypic
Neurodevelopmental Cohort (PNC) further confirmed the stability of the results across age ranges (SI Appendix, Results III and IV and Fig. S5).

Since left–right homologs share developmental precursors, a high degree of left–right symmetry is also expected in neuroanatomical phenotypes with early developmental origins. Such left–right symmetry was observed in maps of \( L_\rho \). Quantitatively, this symmetry was demonstrated using phenotypic \( L_\rho \) projected on the CIVET surface, which unlike FreeSurfer has a one-to-one mapping from left hemisphere vertices to right hemisphere. Across vertices, the left–right correspondence was substantial (\( r = 0.79; P_{\text{spin}} < 0.001 \)). Zooming in on the “local correspondence” (37) (the correlation within a demarcated region spanned by a 10-mm geodesic distance), there were large areas where \( r \geq 1 \) (SI Appendix, Fig. S6) and no areas where local correspondence was consistently negative—although local correspondence was lower in prefrontal cortex and the temporal-parietal junction, and higher on average in sulci compared to gyri. The high degree of observed left–right symmetry was suggestive of early developmental origins of the biological processes that drive local correlations in cortical thickness.

The pattern of \( L_\rho \) was also robust to methodological choices in the data analysis pipeline (see SI Appendix, Fig. S4). There was reasonably high anatomical correspondence between maps of \( L_\rho \) regardless of the degree of anatomical smoothing used during image processing (25- vs. 10-mm full-width at half-maximum smoothing kernels in FreeSurfer; \( r = 0.36, P_{\text{spin}} < 0.001 \)). Similary, there was a reasonable correspondence between alternative preprocessing pipelines (FreeSurfer vs. CIVET), indicating a robustness to the diverse subroutines used in these pipelines (\( r = 0.31, P_{\text{spin}} < 0.006 \)). The largest differences between the pipelines were located in the precunes (\( L_\rho \) lower in CIVET) and in the inferior occipitotemporal gyri (\( L_\rho \) lower in FreeSurfer). Finally, the pattern of \( L_\rho \) was robust to two approaches for quantifying a vertex’s local neighborhood, whether the neighborhood comprised the six adjacent vertices on the cortical mesh or all of the vertices within a 10-mm geodesic distance (\( r = 0.68, P_{\text{spin}} < 0.001 \)). Because it is based on a larger amount of data, the distance-based neighborhood is expected to have a higher signal-to-noise ratio. Subsequent results are therefore based on phenotypic \( L_\rho \) calculated using FreeSurfer processing of HCP data with a 25-mm smoothing kernel and a 10-mm geodesic neighborhood. Overall, the degree of replicability in the pattern of results increases our confidence that our findings do reflect an underlying biological process.

Relationship with Gyral–Sulcal Patterns. If the cortical pattern of shared genetic influences on cortical thickness did relate to cortical folding, we would predict an anatomical correspondence between these maps and folding patterns. As hypothesized, the pattern of \( L_\rho \) corresponded with sulcal/gyral organization, especially in primary somatomotor, superior temporal/insular, and cingulate areas. In other words, relatively homogeneous areas of high or low \( L_\rho \) appeared to occur along anatomical regions demarcated by sulcal or gyral boundaries (38), with greater variability in \( L_\rho \) when transversing sulcal or gyral boundaries. Moreover, peaks and valleys of local correlations tended to occur in sulcal fundi or gyral crests, indicating a relationship between \( L_\rho \) and folding. Visual verification of this relationship was confirmed via highly magnified projections onto cortical flat maps at the regional level (Fig. 3). Quantitatively, this result was confirmed when modeling folding via mean curvature (which is positive in outwardly curved sulci and negative in inwardly curved gyri). There was a global correspondence between \( L_\rho \) and mean curvature (\( r = -0.28, P_{\text{spin}} < 0.001 \)), indicating that \( L_\rho \) tended to be lower in sulci and higher in gyri (Fig. 4A and B).

The relationship with curvature was also preserved in a child-hood sample from the PNC (\( r = -0.32, P_{\text{spin}} < 0.001 \);
which was defined as the axis of minimum change in sulcal depth. This axis provided a consistent frame of reference relative to folding throughout the cortical mantle. Axial correlations were parallel to (“along”) this axis, tangential correlations were perpendicular to (“across”) this axis, and $O_P$ was defined as the normalized difference between axial and tangential correlations. Local correlations along the sulcal or gyral axis differed in strength compared to local correlations tangential to these axes, reflected by a remarkable pattern of variation in $O_P$ across the cortex (SI Appendix, Fig. S9 A and B). Overall, anatomical correspondence was low between $O_P$ and mean curvature ($r = 0.05$, $P_{\text{spin}} > 0.5$). The spatial heterogeneity in anatomical correspondence between $O_P$ and mean curvature was captured by local correspondence, which showed significant clusters of positive local correspondence bilaterally in the central sulcus and precentral gyrus, suggesting relatively a greater axial orientation in sulcal fundus. In addition, there was a significant cluster of negative local correspondence along the marginal sulcus in the left hemisphere, suggesting relatively higher tangential orientation in the sulcal fundus; SI Appendix, Fig. S9 C and D). Overall, $O_P$ had a complex spatial neuroanatomical profile.

Discussion

The colocalization of folding with local genetic influences on cortical thickness is a significant contribution to existing models of cortical folding, which have difficulty in explaining the stereotyped location of certain gyri and sulci (17). Patterened, local correlations in cortical thickness may capture the genetic coordination of microstructural properties that constrain cortical folding. The importance of such local correlations in cortical thickness is predicted by previous neuroimaging studies, but prior investigations of thickness covariability focus on correlations between regions across the entire brain (39, 40). At this scale, shared genetic influences tend to be much stronger on average at short distances (30), consistent with the prediction that evolutionary pressure decreases distances between highly connected brain areas to decrease metabolic and wiring costs (41). The topographical variation of local correlations reported in the present study greatly expands upon these prior results. We propose that the observed differences in local correlations track differences in the development of cortical thickness, which may contribute to the emergence of stereotyped cortical folding. There is prior support for the fact that genetic correlations in

SI Appendix, Results IV and Fig. S5) and when using a “centering” alternative to smoothing, where the average thickness within 5 mm of a vertex was correlated with the average thickness at a distance of 5 to 7 mm to estimate $L_P$ ($r = -0.30$, $P_{\text{spin}} < 0.001$; SI Appendix, Results II and Fig. S7). This anatomical correspondence is consistent with the hypothesis that patterned genetic influences on cortical thickness influence patterns of cortical folding in the developing brain.

Since the locations of folding are stereotyped only in a subset of sulci, with greater intersubject variability in the locations of other sulci thought to be under looser genetic control, the degree of anatomical correspondence between folding and $L_P$ should also be spatially heterogeneous. This spatial heterogeneity was captured by the local correspondence, which showed specific areas of high-magnitude correspondence between mean curvature and $L_P$ (Fig. 4 C and D). This correspondence tended to be negative in sulci, indicating lowest $L_P$ in the sulcal valley where mean curvature is most positive. Using a cluster-based implementation of the spin test, seven clusters bilaterally were statistically significant ($P < 0.05$, familywise correction for multiple comparisons). All of these clusters were composed of negative correspondence within sulci. Prefrontal cortex, an area of the brain enriched for relatively high intersubject variability in sulcal locations, was notable in having relatively low local correspondence with mean curvature. On visual inspection, this finding is consistent with the observation that $L_P$ in prefrontal cortex is relatively high but also relatively spatially uniform within this area of cortex, without the kind of sulcal–gyral variability observed elsewhere in the brain.

Orientation of Local Correlations. In theory, spatial heterogeneity in local correlation could be limited to the average strength of local correlations. Alternatively, a relationship with folding would be supported by differential strength of correlations in different directions relative to sulcal fundi or gyral crests. These differences in the local “correlation orientation” ($O_P$) were quantified relative to the sulcal/gyral axis (SGA) at each vertex,
cortical thickness, and the phenotypic correlations to which they are closely related, reflect coordinated changes in thickness in neurodevelopment (42, 43) and arise from spatial gradients of signaling molecules (29). At the cellular level, thickness may relate to the size of and number of neurons in cortical columns, which partially dictate the function of different cortical areas (1, 44, 45). Moreover, biomechanical models have clearly demonstrated that thickness influences folding, with increased average thickness expected to result in wider folds (13). To our knowledge, the biomechanical effect of stereotyped spatial variation in thickness is unexplored but could plausibly influence the localization of folding in neurodevelopment; the latter comprises a testable prediction for future biomechanical studies. Zones of low average correlation may reflect gradient boundaries in terms of different growth factors influencing alternative development of cortical thickness on either side of the boundary. These boundaries represent plausible anchor points for folding, which is supported by their correspondence with primary sulci in the present work. The plausibility of the proposal that different factors influence thickness in sulci vs. gyri is consistent with differences in the laminar basis of sulcal and gyral thickness; gyri are on average thicker than sulci, and this increased thickness disproportionately stems from expansion of deep cortical layers that disproportionately project to subcortex as opposed to other cortical areas (1, 44).

It is important to note possible alternative explanations for our empirical findings. We argue that the physical effects of thickness on a folding surface may anchor folding patterns. However, thickness also reflects aspects of cellular composition and the extracellular matrix (46), which may independently affect cortical stiffness and thereby folding (13). Finally, the observed correspondence could result from an alternative influence of folding on thickness, or a third variable that emerges subsequent to cortical folding in neurodevelopment. Critically, we demonstrate that the correspondence between local correlations and curvature is preserved in a childhood sample aged 8 to 9, supporting their correspondence with primary sulci in the adult human brain. These patterned maps may reflect local signaling gradients that provide a spatial template for cortical folding patterns during early development, by influencing cortical thickness and the biomechanical properties of local tissue. Disruption of these gradients may in turn underlie folding disruption in developmental neuropsychiatric disorders.

Materials and Methods

Study Sample, Image Acquisition, and Data Availability. The GOBS, HCP, and PNC datasets have been described in detail in prior publications (30, 32–34). The GOBS consists of high-resolution MRI in 1,443 discordant twin pairs (606 females; age mean, 40.7; SD, 15.5; range, 18 to 85) from randomly ascertained extended pedigrees of Mexican American individuals living in San Antonio, Texas. The HCP is a publicly available resource and consists of MRI data from 1,113 individuals (606 females; age mean, 28.8 y; SD, 3.7; range, 22 to 37) from 457 unique families. Image processing used FreeSurfer, version 5.3 (56–58). Cortical thickness was calculated as the distance between the gray-matter and pial surfaces at each vertex. The average of cortical folding, was defined as the average of the principal curvatures at each vertex (31). For comparison, the Montreal Neurological Institute CIVET pipeline (version 1.1.10) was also used to calculate cortical thickness on the HCP sample, as previously described (59). For fidelity of comparison to FreeSurfer surfaces, this mesh was down-sampled to 9,885 uniform cortical regions by merging triangular faces into single regions (where the thickness calculation was the mean thickness of the thin-averaged region). See SI Appendix, Methods I and Results IV for further details.

The HCP data used in this study are available to investigators deemed to have a legitimate research use according to the Restricted Access Data Use Terms described at https://www.humanconnectome.org. The PNC data are available through dbGaP (phs000607.v1.p1). The genotype data for GOBS participants are available through dbGaP (phs001215.v2.p2). The GOBS imaging phenotypes used in this study are available from the National Institute of Mental Health Repository (https://www.nimhgenetics.org). Alternatively, data from the GOBS cohort can be applied for by contacting D.C.G. (david.glahn@childrens.harvard.edu) or J.B. (john.blangero@utrgv.edu). Access to data by qualified investigators is subject to ethical and scientific review (to ensure the data are being requested for valid scientific research) and must comply with all relevant guidelines. The completion of a material transfer agreement signifies that the investigator has met the institutional requirements. All GOBS participants provided informed consent, and the study was approved by institutional review boards at Yale University and the University of Texas Health Science Center at San Antonio. Code used for analyses presented in this paper is available at https://github.com/aaronab.

Local Correlations of Cortical Thickness. Informed by familial information from extended pedigrees, SOLAR (60) was used to confirm significant heritability of cortical thickness at each vertex, as well as to decompose the phenotypic correlation (ρ) into the environmental correlation (ρE) and the genetic correlation (ρG) between neighboring vertices on the cortical mesh. ρ is equivalent to the “structural covariance” between vertices, while ρG is an estimate of the proportion of the shared variance due to shared genetic factors (see SI Appendix, Methods II–III for further details). Age, age2, sex, and total brain volume were also included as covariates in these models.

Two methods were used to determine a vertex’s local neighborhood: in the first method, adjacent vertices on the triangular cortical surface (∼6 neighbors per vertex); in the second method, vertices within 10 mm of a vertex, calculated using geodesic distance on the triangular mesh (∼30 neighbors per vertex). The nonlinear relationship between the local correlations between neighboring vertices and the anatomical distance between these vertices across the cortical surface was regressed from the strength of these correlations (after r-to-z transformation) using generalized additive models in the R package gam (61), and the residuals after this step were used in all subsequent analysis. This regression step is necessary as smoothing is
imposed by image processing pipelines for the purposes of spatial normalization, which could result in spurious correlations (see SI Appendix, Results II for further detail). The correlation between an individual vertex and each of the vertices in its neighborhood was averaged to yield $L_V$.

**The Orientation of Local Correlations.** We also quantified a measure of anisotropy in a vertex’s $L_V$ (higher correlations along a specific directional axis), which we labeled the “orientation of correlation” ($O_P$) (Fig. 1C). To find $O_P$ at each vertex, $v$, we first estimated the orientation of the SGA at $v$. The SGA provided a biologically meaningful frame of reference throughout the cortical mantle, whereby directions parallel to (“along”) the SGA at a vertex are defined as axial, while directions perpendicular to (“across”) the SGA are defined as tangential. Then, the axial correlation ($L_{aP}$) is the correlation in the axial direction, quantified as the average of correlations within 30 degrees of SGA; the tangential correlation ($L_{tP}$) is the correlation in the tangential direction, quantified as the average of the correlations within 30 degrees of the direction that is orthogonal to SGA. The vertex’s orientation is defined as follows: $O_P = (L_{aP} - L_{tP}) / \text{sd}(L_{aP})$, where $\text{sd}(L_{aP})$ is the SD of all of the vertex’s correlations. Intuitively, a highly positive $O_P$ corresponds to a vertex with an axial orientation, a highly negative $O_P$ corresponds to a vertex with a tangential orientation, and $O_P = 0$ corresponds to a relatively isotropic orientation. See SI Appendix, Methods III for further information.

**Statistical Testing of Anatomical Correspondence.** The global anatomical correspondence between two maps, such as those of genetic and phenotypic $L_V$ was quantified using a previously described randomization procedure (the “spin test”) (25). Here, the null hypothesis is that the observed correspondence is due to a random alignment between the maps that is no greater than is expected by chance. This null is operationalized by randomly rotating one map relative to the other map and recalculating the measure of correspondence. See SI Appendix, Fig. 53 for an illustration of this procedure. Local correspondence was quantified using a method similar to the previously described approach of “local cortical coupling” (27). In brief, this procedure quantifies the correspondence between two surfaces, within a demarcated local area around each vertex—a sliding 10-mm geodesic window, only including points within 10 nm of that vertex. The statistical significance of local correspondence was quantified using cluster-based version of the spin test, which rejects the null hypothesis of no local correspondence for clusters of vertices while controlling for multiple comparisons. See SI Appendix, Methods IV for further information.

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Alexander-Bloch et al.
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