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Subject-level measurement of local cortical coupling

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ABSTRACT

The human cortex is highly folded to allow for a massive expansion of surface area. Notably, the thickness of the cortex strongly depends on cortical topology, with gyral cortex sometimes twice as thick as sulcal cortex. We recently demonstrated that global differences in thickness between gyral and sulcal cortex continue to evolve throughout adolescence. However, human cortical development is spatially heterogeneous, and global comparisons lack power to detect localized differences in development or psychopathology. Here we extend previous work by proposing a new measure – local cortical coupling – that is sensitive to differences in the localized topological relationship between cortical thickness and sulcal depth. After estimation, subject-level coupling maps can be analyzed using standard neuroimaging analysis tools. Capitalizing on a large cross-sectional sample ($n = 932$) of youth imaged as part of the Philadelphia Neurodevelopmental Cohort, we demonstrate that local coupling is spatially heterogeneous and exhibits nonlinear development-related trajectories. Moreover, we uncover sex differences in coupling that indicate divergent patterns of cortical topology. Developmental changes and sex differences in coupling support its potential as a neuroimaging phenotype for investigating neuropsychiatric disorders that are increasingly conceptualized as disorders of brain development. R code to estimate subject-level coupling maps from any two cortical surfaces generated by FreeSurfer is made publicly available along with this manuscript.

Introduction

To accommodate a marked expansion of surface area, the cortical sheet of the human brain is highly folded (Van Essen, 1997; Zilles et al., 2013). Such folding has important functional implications and may increase computational efficiency due to reduced axonal distance within a gyrus (Van Essen, 1997). Moreover, folding patterns and local cortical thickness are closely inter-related (Fischl, 2013; von Economo, 1925). von Economo (1925) described that the thickness of the cortex is significantly reduced in passing from the crown of a gyrus to the floor of a sulcus. This striking relationship was subsequently verified *in vivo* using structural neuroimaging techniques (Fischl and Dale, 2000).

It was long posited that this relationship between sulcal depth (SD) and cortical thickness (CT) is established *in utero* or in the perinatal period simultaneously with the development of cortical convolution (Toro and Burnod, 2005; von Economo, 1925; Zilles et al., 1997). However, we recently demonstrated that the relationship between CT and SD evolves dynamically throughout youth (Vandekar et al., 2015). Notably, topological position influences cortical maturation throughout this critical period. We found that linear thinning is widespread across the cortex but is maximal in the depths of the sulcus, whereas circumscribed areas of gyral cortex demonstrate marked nonlinear thickening between the ages of 8 and 14 years (Vandekar et al., 2015).

This work established that understanding relationships between cortical measures (e.g., thickness and depth) is critical for an accurate characterization of the plastic remodeling that occurs during youth. Furthermore, it suggests that such brain phenotypes may be important to understanding neuropsychiatric disorders (schizophrenia, autism, ADHD) that are increasingly conceptualized as disorders of brain development (Insel, 2010; Krain and Castellanos, 2006; Rapoport et al., 2012; Shaw et al., 2012; Steen et al., 2006; White et al., 2003) and may occur on a localized scale (Ronan et al., 2012; Wagstyl, 2015).

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There are important methodological considerations in trying to relate the properties of two cortical surfaces or volumetric brain images: cortical surfaces and brain images are highly autocorrelated, non-independent measures that can be re-sampled to an arbitrary number of observations. Thus, standard parametric statistics are not applicable. Prior work used canonical correlation analysis (Avants et al., 2010; Ouyang et al., 2015) to describe the relationship between two measures in volumetric space. In order to assess the significance of the observed correlation, Avants et al. (2010) relied on permutation tests that relabeled subjects. This approach seeks to understand the relationship between the two measures across subjects. In our recent work (Vandekar et al., 2015), we introduced a novel spatial permutation testing procedure, adapted from the field of microscopy research, that evaluates the relationship between cortical measures in a statistically rigorous framework. Our approach differed from Avants et al. in that the interest was in assessing the spatial relationship between two variables within two averaged cortical surfaces. While this approach successfully delineated robust spatial effects associated with development in youth, it was limited in that analyses studied only global effects *across subjects*. For studies of more subtle individual and group differences in spatial relationships such an approach is not ideal, as it does not allow exploration of local regional effects. A *within-subject* map describing the spatial relationship among cortical measures would be a substantial advance and allow the application of standard tools for group-level analysis (e.g., GLM, MVPA, etc.) across subjects.

Here we introduce a method for describing local *cortical coupling* on a *within-subject* basis using a surface-based, locally-weighted regression procedure. Although this procedure could be used for any two surface maps, we apply it to extend our prior work describing how changes in CT are coupled to SD in development. We capitalize on the Philadelphia Neurodevelopmental Cohort (PNC), a large-scale, single-site study of brain development (Calkins et al., 2015; Satterthwaite et al., 2015, 2014a). Results demonstrate that local coupling is developmentally relevant and specific to regions where the relationship between CT and SD is evolving. We further illustrate the measure's applicability to studies of individual and group differences by demonstrating the presence of substantial sex differences in cortical coupling. Finally, we provide publically available R code (https://bitbucket.org/simonvandekar/coupling) for the estimation of coupling of Freesurfer surfaces as a resource for the neuroimaging community.

Methods

Subjects

Subjects included 932 youths (504 females) aged 8–22 (mean = 14.8; sd = 3.6) who completed neuroimaging as part of the PNC. The Institutional Review Boards of Penn and the Children's Hospital of Philadelphia approved all study procedures. All study participants provided informed consent; minors under age 18 provided assent and the parent or guardian provided consent. The sample, screening, and quality assurance procedures were previously detailed (Satterthwaite et al., 2014a; Vandekar et al., 2015).

Briefly, this study considered 1445 subjects imaged as part of the PNC. Of this sample, 332 subjects met exclusionary criteria due to a history of potential abnormalities in brain development: medical problems that may affect the brain ($n = 166$), inpatient psychiatric hospitalization ($n = 51$), or current use of psychotropic medication ($n = 165$). Two hundred thirty-nine subjects met image quality assurance exclusionary criteria that included an automated and manual screening. Many subjects were excluded due to multiple of the listed criteria, yielding the 932 subjects included in the present analysis and also used in our prior report (Vandekar et al., 2015). Quality assurance screening was based only on the standard Freesurfer output; no additional screening was made on the estimated cortical coupling maps. That is, if the data quality is suitable for the analysis of standard cortical measures (e.g., thickness and sulcal depth), then it should be suitable for analyses of coupling estimated from these measures.

Image acquisition and preprocessing

Image acquisition, preprocessing, and cortical reconstruction steps are as described in Vandekar et al. (2015). A magnetization-prepared, rapid acquisition gradient-echo (MPRAGE) T1-weighted structural image was acquired, using the following parameters: TR, 1810 ms; TE, 3.51 ms; FOV, 180 × 240 mm; matrix, 192 × 256; 160 slices; TI, 1100 ms; flip angle, 9°; effective voxel resolution, 0.9375 × 0.9375 × 1 mm; and axial acquisition plane (Satterthwaite et al., 2014a).

Cortical reconstruction was performed using Freesurfer 5.3.0. Freesurfer processing includes intensity normalization, gray and white matter segmentation, tessellation of the pial and gray/white matter boundaries, and spherical registration to a template (Dale et al., 1999), ultimately producing CT and SD surface maps (Dale et al., 1999; Fischl et al., 1999) which were used to estimate coupling for each subject. Cortical thickness is estimated in Freesurfer as the shortest distance between the estimated gray/white and pial surfaces. SD is estimated by the formula

$$\int \mathrm{n}(k)^T \frac{\partial J}{\partial x_k^t} dt,$$

where $\mathrm{n}(k)^T$ is the surface normal vector at vertex k, $\frac{\partial J}{\partial x_k^t}$ is the gradient of J with respect to x_k at time t, and J is a cost function for the inflation of the cortical surface that is based on the distance of each vertex from its neighbors. SD measures the distance a given vertex moves outward during the inflation process. Prior to Freesurfer 6 the units of sulcal depth are in arbitrary units. Other proposed methods for investigating SD use different geometry for estimating SD (Yun et al., 2013), or allow for comparison of SD in subject space using automatically labeled neuroanatomical regions of interest (Mangin et al., 2004). The pointwise calculation of SD in Freesurfer allows for estimation of coupling in template space.

After estimation of CT and SD, surface maps were registered to the fsaverage5 template using the standard spherical registration procedure in Freesurfer (Fischl et al., 1999). The fsaverage5 template was used to decrease the time to estimate coupling and reduce the number of comparisons conducted.

Estimation of coupling maps

Local CT–SD coupling is a subject specific measure that is estimated at each vertex on the cortical surface in template space. The measure is intended to capture one aspect of the multivariate nature of cortical measurements; specifically, coupling describes the localized relationship between CT and SD in a neighborhood of a given vertex.

For CT and SD, the coupling measure at a given vertex, v_0, is defined as the slope parameter estimate of a weighted regression of CT onto SD in a neighborhood, N_{v_0}, of v_0 (Fig. 1). The weights in the regression are related to the neighboring vertices' distance from the central vertex.

Distance is defined as the Euclidean distance between points on the surface. We allow neighbors up to 15 degrees of separation. Weights are all less than or equal to one and rounded to three decimal places. To minimize interpolation through the surface, weights for neighbors of the same order as a neighbor with a weight of zero are all set to zero. The weights, w_j, used in the regression are proportional to the standard normal probability density function,

$$\mathrm{w_j} = \mathrm{e}^{\left(-\frac{1}{2\sigma^2}\mathrm{d}(\mathrm{v_0},\mathrm{v_j})^2\right)}$$

where σ is a parameter that can be changed to modify the smoothness of the surface by adjusting the weights in the regression. A larger