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Structural asymmetry of the human cerebral cortex: Regional and between-subject variability of surface area, cortical thickness, and local gyrification

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A B S T R A C T

Structural asymmetry varies across individuals, brain regions, and metrics of cortical organization. The current study investigated regional differences in asymmetry of cortical surface area, thickness, and local gyrification, and the extent of between-subject variability in these metrics, in a sample of healthy young adults ($N=200$). Between-subject variability in cortical structure may provide a means to assess the extent of biological flexibility or constraint of brain regions, and we explored the potential influence of this variability on the phenotypic expression of structural asymmetry. The findings demonstrate that structural asymmetries are nearly ubiquitous across the cortex, with differing regional organization for the three cortical metrics. This implies that there are multiple, only partially overlapping, maps of structural asymmetry. The results further indicate that the degree of asymmetry of a brain region can be predicted by the extent of the region's between-subject variability. These findings provide evidence that reduced biological constraint promotes the expression of strong structural asymmetry.

1. Introduction

Asymmetry of function is a hallmark feature of brain organization in the human cortex. It is sometimes claimed that structural cerebral asymmetries are small and of minor significance compared to strong and prominent functional asymmetries (e.g., Wey et al., 2014). If so, then one would need to argue that functional asymmetries arise primarily from differing patterns of brain activity that are subserved by similar anatomical substrates (e.g., differing functional connectivity networks – see Wey et al. (2014)). While this is not entirely implausible, function tends to parallel form in many areas of biology. Hence it is worth looking closely at a variety of neurostructural measures before concluding that structural bases of hemisphere asymmetries are lacking. Asymmetries can be found at multiple spatial scales (cytoarchitecture, cortical morphometrics, structural networks within and across hemispheres). In the current investigation, we examine asymmetries of cortical surface area, thickness, and local gyrification in a relatively large sample of healthy young adults. We find that structural asymmetries vary from region to region but are ubiquitous across all measures of cortical organization, suggesting that these structural features can provide a platform for the emergence of functional hemisphere differences.

Individual variability is an important component of biological systems. Hence, some significant variability in structural asymmetry is to be expected across different brain regions, as well as across individuals within the same region. Regional differences in asymmetry of surface area (Kang et al., 2012; Koelkebeck et al., 2014; Van Essen et al., 2012) and cortical thickness (Koelkebeck et al., 2014; Plessen et al., 2014; Zhou et al., 2013) have been reported, and a few prior studies have reported between-subject variability in regional cortical volume (Kennedy et al., 1998) or thickness (Mueller et al., 2013). However, there has been no consideration of the relationship between these two indices of variation. In other words, are brain regions with high between-subject variability more or less likely to be strongly asymmetrical at the population level? Answering this question may provide insight into why some regions are more asymmetrical than others, as discussed further below. In the current investigation we explore both regional and individual variation in the morphometry of left and right cortex, and investigate whether the degree of asymmetry of a given region may be predicted by the extent of its phenotypic variation.

1.1. Prior research on macrostructural asymmetries

In the modern era, consideration of structural asymmetries was initiated by Geschwind and Levitsky's (1968) discovery, using post-mortem data, of prominent leftward asymmetry of the

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planum temporale. With the advent of MRI scans, these findings were replicated by identifying sulcal landmarks to delineate specific regions, and then manually tracing serial sections to estimate the surface area of the region. Using these methods, planum temporale asymmetries were replicated many times, and some additional perisylvian regions were shown to be asymmetrical (e.g., leftward asymmetry of Heschl's gyrus, rightward asymmetry of the planum parietale) (Chiarello et al., 2004; Foundas et al., 2002; Shapleske et al., 1999). However, the need to individually identify anatomical landmarks and manually trace each region on serial MRI sections precluded the analysis of asymmetries across the entire brain and tended to limit sample size.

Automated methods are now available to measure asymmetries across the entire cortex, enabling substantially larger samples to be examined. Further, surface based methods permit estimation of multiple aspects of cortical structure (surface area, thickness, gyrification) (Dale et al., 1999; Fischl et al., 1999a; Schaer et al., 2008). It is widely acknowledged that cortical surface area (tangential extent), thickness (radial extent), and gyrification (surface area folding) can vary independently of each other (Wallace et al., 2013), and differ in their genetic bases (Panizzon et al., 2009; Winkler et al., 2010), network structure (Sanabria-Diaz et al., 2010) and developmental trajectories (Hogstrom et al., 2013; Raznahan et al., 2011). Understanding the structural basis of cerebral asymmetry will require exploration of asymmetries for each metric, as well as how the various indices of asymmetry relate to each other.

Two general approaches have been used to examine asymmetries across the entire cortex.[1] In one approach, point-to-point comparisons across left and right hemispheres are made which requires complex matching algorithms to determine corresponding points despite hemisphere differences in cortical surface anatomy (Luders et al., 2006; Plessen et al., 2014; Van Essen et al., 2012). After correction for multiple comparisons, a whole-brain asymmetry map is then constructed. Here measurement precision is optimized, but quantitative values for asymmetry of specific regions are not provided. A second approach uses sulcal boundaries to independently demarcate regions within each hemisphere, and then left/right asymmetries are computed for each a priori identified region (Koelkebeck et al., 2014). This second approach is similar to traditional anatomical methods, but eliminates the need for human identification of anatomical regions and manual measurements. The FreeSurfer analysis suite (Dale et al., 1999; Fischl et al., 1999a; Fischl et al., 1999b) provides a standardized method for parcellating the cortex, simplifying quantitative comparisons across studies with reference to common anatomical atlases (Desikan et al., 2006; Destrieux et al., 2010). However, the sulcal boundaries used to parcellate the cortex may not represent the optimal means to reveal regions with differing asymmetries, as values are summed or averaged across all vertices/voxels within each region. Nevertheless, although early cytoarchitectural work emphasized the lack of correspondence between cytoarchitectural and sulcal boundaries (Amunts et al., 1999), more recent findings indicate that, for many brain regions, sulci boundaries provide reasonable indications of cytoarchitectural transitions (Fischl et al., 2008; Weiner and Zilles, 2015).

Van Essen et al. (2012) examined *surface area* asymmetries on a point-to-point basis from a variety of published data sets (various age groups) and noted statistically significant asymmetries across approximately 2/3 of the cortex. Leftward asymmetries included posterior perisylvian regions, ventromedial and anterior temporal areas, insula, mid-to-posterior cingulate, medial and lateral parietal, and some lateral frontal regions. Prominent rightward asymmetries were observed near the angular gyrus and dorsomedial prefrontal cortex with additional rightward asymmetries in lateral temporal, occipital, and orbitomedial prefrontal cortex.

Three additional studies employed varying methods to investigate point-to-point cortical *thickness* asymmetries across the entire adult brain. Luders et al. (2006) examined 60 young adults and observed thicker left than right cortex in the ACC, anterior temporal and prefrontal cortex, precentral and supramarginal gyri. Rightward thickness asymmetries were observed in the IFG, lateral posterior ITG, precuneus and lingual gyrus. Two other investigations examined age-related changes in cortical thickness asymmetry from childhood to late middle age (Plessen et al., 2014; Zhou et al., 2013). Both studies found region-specific changes in asymmetry with age, however the presentation of the data does not allow regional comparisons of their young adult participants to those studied by Luders et al. (2006) or the current investigation.

Several previous studies have reported automated parcellation-level asymmetries within specific regions of interest (e.g., surface area of language areas – Chiarello et al., 2013; thickness and surface area of auditory cortex – Meyer et al. (2014)). Only one prior study has investigated surface area and cortical thickness asymmetries across the entire adult brain using an automated parcellation approach (Koelkebeck et al., 2014). In this study MRI scans from 101 Japanese individuals (mean age 33.3 yrs) were parcellated into 33 brain regions using the Desikan et al. (2006) atlas. In this study leftward *surface area* asymmetries were found in the pars opercularis, Heschl's gyrus, temporal pole, and entorhinal cortex, and lateral occipital cortex, postcentral gyrus, SFG, caudal MFG, and rostral ACC. Rightward area asymmetries were observed in the IFG, several medial regions, MTG, inferior parietal and frontal pole. For cortical *thickness*, leftward asymmetries were found through most regions of the cingulate cortex, and rightward asymmetries were obtained in the IFG, several temporal regions (temporal pole, STS, MTG, Heschl's gyrus), as well as entorhinal and lateral occipital regions. Negative correlations were obtained between surface area and thickness asymmetries in many regions. This study demonstrated that surface area and cortical thickness yield differing, and often opposing, patterns of asymmetries, implying that that more than one neurobiological mechanism may underlie the lateral organization of the brain. Unfortunately, the parcellation scheme employed by Koelkebeck et al. (2014) did not yield a separate measure for the planum temporale, nor for gyral vs sulcal cortex that are known to differ anatomically (Deng et al., 2014; Fischl and Dale, 2000; Nie et al., 2012).

Prior studies document surface area and cortical thickness asymmetries throughout the adult cortex, although variations in methods and subject populations make comparisons across studies difficult. Only one investigation explored two metrics of cortical structure in the same group of participants (Koelkebeck et al., 2014), permitting cross-metric correlation of asymmetry. Furthermore, gyrification asymmetries have not been thoroughly explored. Although gyrification increases as cortical surface area expands, both phylogenetically and ontogenetically (Zilles et al., 2013), there is evidence that groups can differ in regional gyrification, despite having similar surface area in the same regions (Wallace et al., 2013; McDowell et al., in press). Hence, it is important to independently investigate surface area and gyrification asymmetries. The current study investigates surface area, thickness, and gyrification asymmetries in the same sample of healthy young adults using a regional parcellation approach.

1.2. Prior research on regional differences in variability of cortical morphometry

Individual differences in cortical morphometry are sometimes dismissed as "noise" – perhaps reflecting measurement error or

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[1] Volumetric approaches have also investigated brain-wide structural asymmetries (e.g., Watkins et al., 2001). However, because cortical volume is the product of surface area and thickness that have independent biological bases, we limit our review to prior surface based studies.