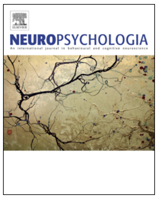
Neuropsychologia 93 (2016) 350–364

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia



Regional correlations between cortical thickness and surface area asymmetries: A surface-based morphometry study of 250 adults

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ARTICLE INFO

Article history:
Received 11 November 2015
Received in revised form
21 March 2016
Accepted 23 March 2016
Available online 25 March 2016

Keywords:
Surface-based morphometry
Structural asymmetry
Cortical thickness
Cortical surface area
Sulcal depth
Regional correlation
Handedness

ABSTRACT

We report on the patterns of asymmetries of various MRI-derived cortical phenotypes, namely cortical thickness (CT), cortical surface area (CSA), cortical volume (CV) and sulcal depth (SULC), as well as on their cross-relationships. A surface-based approach was designed to obtain cortical asymmetry maps unbiased for inter-hemispheric structural positional misalignment. Accurate vertex-wise asymmetries of CT, CSA, CV, and SULC were so obtained in 250 individuals including 120 left-handers that had been selected from a larger population as having a typical leftward language lateralization. We found no significant effect of handedness on CT, CSA or CV asymmetries, although a trend for a significant difference in the SULC asymmetry of the Rolandic genu was present (leftward in right-handers, rightward in left-handers). At the hemispheric level, we found rightward CT and CSA asymmetries that were not correlated. At the regional level, asymmetry patterns of CT and CSA were marked by a spatial overlap of both concordant and opposite CT and CSA asymmetries. Half of these regions of overlap presented a significant association (positive or negative) between CT and CSA asymmetries. Strikingly, the 3 regions showing positive correlations between CT and CSA asymmetries were those known to exhibit robust asymmetries across methodologies, such as the leftward asymmetrical *planum temporale* and the rightward asymmetrical superior temporal sulcus and cingulate cortex. This study demonstrates that regional correlations between CT and CSA asymmetries are a characteristic of brain structural organization that could be of significance in the choice of structural markers in studies dealing with the genetic basis of brain lateralization.

1. Introduction

The two hemispheres of a human brain may seem similar at first sight, but they are actually not symmetrical in terms of either structure or function (see Hervé et al. (2013) for a review). The most prominent brain asymmetry is related to the so-called brain Yakovlevian anti-clockwise torque, associated with the left occipital and right frontal *petalia*, which corresponds to a greater protrusion of the right over the left frontal lobe and a greater protrusion of the left over the right occipital lobe (Good et al., 2001; Toga and Thompson, 2003; Takao et al., 2011). This asymmetrical brain shift creates positional structural asymmetries between the left and the right hemisphere. For instance, the right posterior ascending ramus of the Sylvian fissure curves upward more anteriorly than does the same structure in the left hemisphere (Witelson and Kigar, 1992; Lyttelton et al., 2009; Glasel et al., 2011). Conversely, the supramarginal and angular gyri are more posteriorly located in the left hemisphere (Van Essen et al., 2012). The more posterior leftward ascending termination of the Sylvian fissure is related to the leftward asymmetry of the *planum temporale* (PT), an original finding by Geschwind et al. upon examination of a sample of 100 post-mortem brains (Geschwind and Levitsky, 1968) that has been consistently reported in further neuroimaging studies (Dorsaint-Pierre et al., 2006; Hervé et al., 2006; Lyttelton et al., 2009; Tzourio-Mazoyer et al., 2010a; Takao et al., 2011; Van Essen et al., 2012; Li et al., 2013; Goldberg et al., 2013; Chiarello et al., 2013; Guadalupe et al., 2014b).

These hemispheric anatomical asymmetries have been shown to appear very early during brain development, being already visible in utero (Dubois et al., 2010; Kasprian et al., 2011; Habas

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http://dx.doi.org/10.1016/j.neuropsychologia.2016.03.025
0028-3932/

et al., 2012; Li et al., 2013). Indeed, during the third trimester of gestation, the initial smooth brain surface becomes highly convoluted (Hill et al., 2010b) and gyrification of the cortex accompanies the cortical expansion, creating gyri and sulci. As early as the 23th gestational week, a leftward interhemispheric folding asymmetry can be observed at the Sylvian fissure site, which hosts the PT at its upper surface (Habas et al., 2012). Moreover, at birth this asymmetry is as great as the asymmetry found in adults (Hill et al., 2010a). The right hemispheric counterpart is the asymmetry of the superior temporal sulcus (STS), which is observed as early as at the 26th gestational week; this rightward asymmetry in sulcal depth remains constant from birth throughout the lifespan (Habas et al., 2012; Glasel et al., 2011; Leroy et al., 2015). The early development of anatomical asymmetries contrasts with those of functional asymmetries that develop much later. Language areas' leftward functional asymmetries, for example, increase linearly with age but are still lower than adult values at 11 years of age (see review in Hervé et al. (2013)).

Voxel-based morphometry (VBM) has been used to measure regional cerebral grey and white matter volume asymmetries in healthy adults (Good et al., 2001; Watkins et al., 2001; Hervé et al., 2006; Takao et al., 2011) and preterm new-borns (Dubois et al., 2010). Results obtained with the VBM approach are very consistent and robust, but the lack of accurate correction for inter-hemispheric differences in sulci position results in asymmetries that are related to both differences in sulci position and tissue compartment volume differences without any possibility of disentangling these two components (Lyttelton et al., 2007). Moreover, VBM analysis captures information about grey matter volume that is, by definition, the product of cortical surface area (CSA) and cortical thickness (CT) and so provides information on structural asymmetries that may be specific to a given anatomical feature.

Recent neuroimaging surface-based methods (SBM) allow the measurement of CSA and CT features independently and both at the local, regional and hemispheric levels. SBM studies have shown that although CSA and CT are both highly heritable, they seem to be unrelated genetically at the global, lobar and regional levels (Panizzon et al., 2009; Winkler et al., 2010; Cai et al., 2014). However, distinct sources of genetic influences do not imply an absence of phenotypic correlation, and Winkler et al. who investigated the correlation between regional CSA and CT from a surface-based parcellation, showed a strong correlation between CT and CSA in regions such as the frontal superior gyrus, the orbitofrontal cortex, the postcentral gyrus and the transverse temporal gyrus (also named Heschl's gyrus, HG). Hogstrom et al. (2013) also examined the dynamic relationships between CSA and CT from a lifespan perspective. They observed that CSA and CT were negatively correlated in a per-vertex general linear model that took into account the age and gender of the participants. By testing three age groups in adults, these investigators reported similar patterns of significant negative correlation between local CSA and CT in areas including the orbitofrontal cortex, the posterior cingulate gyrus, the superior frontal gyrus, and parts of the temporal lobe bilaterally. These last results indicate that during aging there is an increase of local arealization associated with a decrease in CT in a set of regions that remains stable between 20 and 85 years of age. This anti-correlation pattern between CT and CSA suggests that a common neurophysiological mechanism drives this negative relationship. Harasty has proposed that such a mechanism could be related to the expansion of white matter within a gyrus during development, such white matter increase leading to a local expansion of CSA and consequently to a mechanical thinning of the cortex (Harasty et al., 2003). Concerning correlations between asymmetries, previous studies have shown that CSA asymmetries of the PT were due to asymmetries of minicolumn width, spacing and number (Galuske et al., 2000, Chance et al., 2006). Chance also reported leftward microstructural asymmetries in the mid-fusiform gyrus in terms of width of minicolumn and cell size, with larger pyramidal neurons in the left fusiform gyrus albeit without difference of cell density (Chance et al., 2013). Such differential patterns of hemispheric micro-organization could represent one mechanism supporting cortical thickness asymmetries. Other neurophysiological processes known to modulate cortical thickness during lifespan, such as synaptogenesis, spine formation or elimination, dendritic branching or pruning, angiogenesis, gliogenesis and myelination, could also be involved in the establishment of CT asymmetries (Tardif et al., in press), the relative importance of these different factors being an open question.

CT and CSA asymmetry patterns have been investigated mainly with a regions-based approach (Chiarello et al., 2013, in press; Meyer et al., 2013; Koelkebeck et al., 2014; Kang et al., 2015) using different cortical parcellations (i.e., either the Desikan or the Destrieux parcellation included with the FreeSurfer package: Desikan et al., 2006; Destrieux et al., 2010). This approach, however, is limited in terms of spatial resolution in relation to the number and/or size of cortical regions explored. To overcome this limitation, some studies have applied SBM combined with powerful cross-hemispheric structural registration tools for computing vertex-wise asymmetry maps of either CSA (Lyttelton et al., 2009; Van Essen et al., 2012) or CT (Luders et al., 2006; Plessen et al., 2014; Shaw, 2009; Zhou et al., 2013). However, to our knowledge, none of these studies have simultaneously investigated CSA and CT vertex-wise asymmetry maps or their relationships or in the same sample of participants. However, studies on how CT and CSA asymmetries are related to each other would be of great interest, especially for determining optimal brain phenotypes for studies of the genetic basis of brain lateralization (Guadalupe et al., 2014b) as well as for investigating the relationship between anatomical and functional lateralization (Tzourio-Mazoyer et al., 2015).

Here, we addressed this issue, taking advantage of the BIL&GIN (Mazoyer et al., 2015), a multidimensional, multimodal neuroimaging database specifically designed for the study of hemispheric lateralization in a large sample of individuals enriched in left-handers. We implemented a surface-based symmetrization procedure based on a fine interhemispheric structural registration across hemispheres to compute the spatial distribution of anatomical asymmetries of CT, CSA, CV and SULC at the vertex-wise level. The sample selected for the present study was composed of 250 participants of the BIL&GIN (120 left-handers), selected as typical from the results of an fMRI acquisition of language production (Mazoyer et al., 2014). The use of such a large and homogenous sample allows us to report here the pattern of asymmetries of CT and CSA and the spatial and quantitative relationships between these asymmetries. This approach also allowed us to characterize the impact of handedness and brain volume on patterns of cortical asymmetry independently of language lateralization.

2. Material and methods

2.1. Participants: characteristics of the typical sample

The sample of participants has been fully described elsewhere (Mazoyer et al., 2015). Briefly, a sample of 250 healthy individuals, balanced for handedness and sex (130 RH, including 66 women; 120 LH, including 57 women) were included in the present study. A local ethics committee (CCPRB Basse-Normandie) approved the experimental protocol. Participants gave their informed, written consent, and received compensation for their participation in the study. All participants were free of brain abnormalities as assessed by inspection of their structural T1-MRI scans by a trained radiologist. The sample mean age was 25.5 years (S.D.=6.1 years, range: 18–57 years), and the sample mean level of education was 15.5 years ±2.3 years (range: 11–20 years) from elementary school. Handedness was self-reported