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MAPPING GENETIC AND ENVIRONMENTAL INFLUENCES ON CORTICAL SURFACE AREA OF PEDIATRIC TWINS

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Abstract—Cortical surface area has been largely overlooked in genetic studies of human brain morphometry, even though phylogenetic differences in cortical surface area between individuals are known to be influenced by differences in genetic endowment. In this study, we examined the relative contribution of genetic and environmental influences on cortical surface areas in both the native and stereotaxic spaces for a cohort of homogeneously-aged healthy pediatric twins. Bilateral hemispheric surface and all lobar surface areas except the occipital lobes in native space showed high heritable estimates, while the common environmental effect on bilateral occipital lobes reached statistical significance. The proportion of genetic variance for cortical surface areas measured in stereotaxic space was lower than that measured in native space, whereas the unique environmental influences increased. This is reasonable since whole brain volume is also known to be heritable itself and so removing that component of areal variance due to overall brain size via stereotaxic transformation will reduce the genetic proportion. These findings further suggest that cortical surface areas involved in cognitive, attention and emotional processing, as well as in creating and retaining of long-term memories are likely to be more useful for examining the relationship between genotype and behavioral phenotypes.

Key words: magnetic resonance imaging, pediatric twin, cortical surface area, genetic effect, structural equation modeling.

INTRODUCTION

The cerebral cortex is a relatively thin laminar structure so that the number of neurons and cortical columns in various regions is more related to the surface area of those regions than to their thickness. It has been well documented that neurons within the cerebral cortex are organized into ontogenetic columns that run perpendicular to the surface of the brain (Mountcastle, 1997). It has been postulated that the size of the cortical surface area is driven by the number of columns, whereas cortical thickness is influenced by the number of cells within a column (Rakic, 1988). Cortical surface area is directly proportional to the cortical gray matter volume, suggesting that growth of the neocortex is primarily tangential with a repetition of a basic structural element rather than gross alterations in the thickness of the cortex (Rockel et al., 1980; Hofman, 1985; Mountcastle, 1997). Therefore, the remarkable expansion of the cortical surface during evolution is not associated with a corresponding increase in cortical thickness (Kaas, 1987). And, the radial unit model is a working hypothesis that postulates both genetic and environmental mechanisms for establishing the pattern and size of cytoarchitectonic areas during ontogenetic and phylogenetic development (Rakic, 1988, 1995, 2009). In general, a region-based analysis of cortical surface areas must take into account the global effect of head size unlike cortical thickness which is not correlated with total intracranial volume (Pakkenberg and Gundersen, 1997; Im et al., 2008). Nevertheless, the effect of removing brain size differences between subjects needs to be investigated in the heritability study of cortical surface area since whole brain volume is known to be heritable itself (Pennington et al., 2000; Baare et al., 2001; Geschwind et al., 2002).

Human brain magnetic resonance imaging (MRI) studies have suggested that total cerebral volume (Pennington et al., 2000; Baare et al., 2001; Geschwind et al., 2002), and individual gray matter (GM) and white matter (WM) volumes (Geschwind et al., 2002; Wright et al., 2002) are highly heritable. Although it has been reported that individual lobar brain volumes exhibit lower heritability than the whole brain volume, this might be a consequence of poor reliability in regional partitioning rather than any substantial difference in heritability for

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Abbreviations: CLASP, Constrained Laplacian-based Automated Segmentation with Proximities; CSF, cerebrospinal fluid; DZ, dizygotic; FDR, false discovery rate; FLASH, fast low-angle shot; FWHM, full width half maximum; GM, gray matter; MRI, magnetic resonance imaging; MZ, monozygotic; NIMH, National Institute of Mental Health; NVIQ, nonverbal intelligence; P-FIT, parieto-frontal integration theory; QC, quality control; QNTS, Quebec Newborn Twin Study; ROIs, regions of interest; SEM, structural equation modeling; SES, socioeconomic status; VETSA, Vietnam Era Twin Study of Aging; WM, white matter; WPPSI-R, Wechsler Preschool and Primary Scale of Intelligence-Revised.

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these regions (Geschwind et al., 2002). The cortical GM densities of language-associated areas in the left hemisphere were significantly influenced by genetic factors (Thompson et al., 2001), while ventricular volumes and superficial gyral patterns seem to be mediated almost entirely by environmental factors (Bartley et al., 1997; Baare et al., 2001; Wright et al., 2002). Statistical comparisons of the heritability among cortical regions have to be interpreted with caution because the main limitation of small sample size is the lack of power to test for the influence of common environment (Peper et al., 2007). Our previous heritability study of cortical thickness, with the same population as examined in this study, found that left-lateralized genetic and right-lateralized common environmental influences accounted for individual differences in human brain structures (Yoon et al., 2010). A recent heritability study in pediatric twin pairs showed high heritability of intracranial, total brain, cerebellum, and GM and WM volumes, which is consistent with previous adult studies (Baare et al., 2001; Geschwind et al., 2002; Peper et al., 2007, 2009). Twin studies have clearly demonstrated their importance in research for the genetic contributions to the structural variation of brain in this manner, but the majority of previous studies only applied measures of cortical volume, density, or thickness (Glahn et al., 2007; Peper et al., 2007; Schmitt et al., 2007).

It has been shown that there are large phylogenetic differences in cortical surface areas among individuals for those regions where animal studies have previously revealed a genetic influence in surface area (Bishop et al., 2000; Mallamaci et al., 2000). However, regional area has been largely overlooked in genetic studies of the human brain, perhaps due to a lack of a suitable tool for quantifying local, i.e. regional or vertex-wise, area as opposed to making gross estimates of surface area, i.e. for whole brain, hemisphere or lobe. Several recent studies have underlined the utility of cortical surface area as a measure of cortical morphometry since this is directly related to the number and spacing of the cortical column (Barta and Dazzan, 2003; Chance et al., 2008; Lyttelton et al., 2009). It has been demonstrated in animal studies that specific genes are associated with dramatic changes in arealization and expansion of selected cortical regions (Bishop et al., 2000; Mallamaci et al., 2000). A previous study of regional cortical surface area in adult monozygotic (MZ) twins reported that the cerebral hemispheres might be differentially affected by the genetic influences during cortical morphogenesis, with the language-dominant left hemisphere under stronger genetic control than the right (Tramo et al., 1995). However, it is not sufficient to explore genetic and environmental factors without a comparison of twin pairs with different degrees of genetic affinity such as dizygotic (DZ) twins. The most recent study of the genetic relationship between cortical surface area and thickness in middle-aged male twins showed that they were genetically distinct from each other (Panizzon et al., 2009). While the spatial orthogonality of cortical surface area and thickness can be inferred from their geometric relationship, it is insufficient to suggest their biological independence (Winkler et al., 2010). These distinct genetic effects on cortical surface area and thickness might be consistent with the columnar organization of the cerebral cortex and the putative developmental origins of that organization, as specified by the radial unit hypothesis as described above (Rakic, 1988, 1995; Mountcastle, 1997; Panizzon et al., 2009; Rakic, 2009). These results, however, must be validated with pediatric twins owing to the high degree of developmental change in brain tissues during childhood and adolescence (Giedd et al., 1999; Sowell et al., 2004; Jernigan and Gamst, 2005).

In this study, we examined the relative contribution of genetic and environmental influences on vertex- and lobe-based cortical surface areas in a cohort of homogeneously-aged (8-year-old) healthy pediatric MZ and DZ twins, which would be compared with previous regions of interest (ROI) studies. It is expected to provide a better estimation of the genetic and environmental influences on phenotypic variance since younger twin pairs have largely shared a common environment compared with adult ones and studying a homogeneously-aged cohort will reduce the age confound upon the genetic effect of interest. These cortical surface area metrics were obtained in both the native and stereotaxic spaces in order to investigate the global effect of brain size on area heritability. We hypothesized that cortical surface area measured in native space would be more heritable because brain volume itself is heritable (Pfefferbaum et al., 2000; Giedd et al., 2007).

EXPERIMENTAL PROCEDURES

Participants

The pediatric subjects in the present study are enrolled in Quebec Newborn Twin Study (QNTS), an ongoing longitudinal study of twins from the Province of Quebec, Canada, who were recruited at birth between 1 April, 1995 and 31 December, 1998. For same-sex twin pairs, zygosity was reliably assessed with combined use of twins' medical files and a shortened version of Goldsmith's Zygosity Questionnaire for Young Twins (Goldsmith et al., 1999), as well as DNA tests for 8–10 highly polymorphous genetic markers. Zygosity based on the similarity of these genetic markers corresponded at 96% with zygosity based on physical resemblance (Forget-Dubois et al., 2003).

The demographic characteristics of participants in this study are summarized in Table 1. While it has been previously reported that heritability estimates are not significantly affected by sex (Lenroot et al., 2009), only same-sex twin pairs were included in this study with regard to obvious gender differences in the structure of the brain (Giedd et al., 1997; Lenroot et al., 2007;

Table 1. Demographic characteristics of the twin sample

	MZ	DZ
N (boy/girl)	57 (22/35)	35 (15/20)
Age (year)	8.44 ± 0.20	8.47 ± 0.23
Birth weight (kg)	2.42 ± 0.57	2.45 ± 0.49
Gestational age (month)	35.74 ± 2.57	36.64 ± 2.12
NVIQ	102.62 ± 14.25	101.27 ± 14.40
Socioeconomic status	6.72 ± 2.35	6.90 ± 2.30

N: number of same-sex twin pairs.
NVIQ: nonverbal intelligence.