The contribution of genes to cortical thickness and volume

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We analyzed brain MRI data from 372 young adult twins to identify cortical regions in which gray matter thickness and volume are influenced by genetics. This was achieved using an A/C/E structural equation model that divides the variance of these traits, at each point on the cortex, into additive genetic (A), shared (C), and unique environmental (E) components. A strong genetic influence was found in frontal and parietal regions. In addition, we correlated cortical thickness with full-scale intelligence quotient for comparison with the A/C/E maps, and several regions where cortical structure was correlated with intelligence quotient are under genetic control. These cortical measures may be useful phenotypes to narrow the search for quantitative trait loci influencing brain structure. *NeuroReport* 22:101–105 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Brain structure is influenced by both genetic and environmental factors, and their relative influence varies throughout life and differs for different brain regions. As the risk for a variety of neurological and psychiatric disorders is partly inherited, one urgent and achievable research goal is to identify aspects of brain structure and function that are under genetic control, before searching for specific genes that influence them.

Twin studies have been extensively used to estimate the heritability of many cognitive and behavioral traits, and measures derived from brain images. In general, these data sets involve pairs of monozygotic and dizygotic twins; monozygotic twins share 100% of their genes, whereas dizygotic twins share 50% on average. Various methods have been designed to compare the two groups, yielding estimates of the genetic and environmental contributions to various traits, including brain structure.

Here, we studied the influence of genes on cortical thickness and volume; both have been implicated as promising targets for genetic studies. In an early study of 10 monozygotic and 10 dizygotic twin pairs [1], we found regionally varying genetic influences in three-dimensional maps of the heritability of cortical gray matter density – a measure that is correlated with intelligence quotient (IQ). Posthuma *et al.* [2] extended earlier study on gray matter heritability [3–6]. They found that partially overlapping sets of genes were involved in the control of gray and white matter volumes and IQ. Recently, Yoon *et al.* [7] examined the influence of genetic and environmental factors on cortical thickness and volume in 184 8-year-old twins in different brain substructures. In the study by Sullivan *et al.* the authors showed that there were genetic, shared environmental, and individual-specific environmental influences on the volumes of 96 brain regions of interest in 474 middle-aged male twins from the Vietnam Era Twin Study of Aging [6].

However, no large-scale study to date has analyzed genetic contributions to cortical volume and thickness in healthy young adult twins. In this study, we used the A/C/E structural equation model to analyze genetic influences on the brain in a large MRI dataset of twins. We also assessed the relationship between full-scale IQ and cortical thickness at each point on the cortex. This analysis provides a map of significant correlations (P values) between local cortical thickness and full-scale IQ, and involves using mixed effects regression to account for similarities within families [8].

Methods

Data and preprocessing

The data consisted of 372 young adult twins of age 21–27 years (mean age: 23.7 ± 1.9 years, 150 men and 222 women). There were 194 dizygotic and 178 monozygotic twins in the population (37 same-sex male and

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60 same-sex female dizygotic pairs, 32 male and 57 female monozygotic pairs). Opposite sex twin pairs were excluded to prevent sex differences from inflating estimates of genetic effects. Only complete pairs were used for this study.

All twins were scanned using a 4T Bruker Medspec whole-body scanner (Bruker Medical, Ettingen, Germany), at the Center for Magnetic Resonance (University of Queensland, Australia). Three-dimensional T1-weighted images were acquired with a magnetization-prepared rapid gradient echo sequence to resolve anatomy at high resolution.

Acquisition parameters were: inversion time (T_I)/repetition time (T_R)/echo time (T_E) = 700/1500/3.35 ms, flip angle = 8°, slice thickness = 0.9 mm with a $256 \times 256 \times 256$ acquisition matrix. Each participant was informed of the goals of the study and signed a formal consent. The study was approved by the appropriate institutional review and research ethics boards. All participants underwent physical and psychological screening to exclude cases of pathology known to affect brain structure. No twin participants reported a history of significant head injury, a neurological or psychiatric illness, substance abuse or dependence, or had a first-degree relative with a psychiatric disorder. Participants were 21–27 years old and were right handed.

Extracerebral tissues were manually deleted from the MRI images using the Display software from the Montreal Neurological Institute, McGill University, Canada. All scans were then aligned to the ICBM53 template [9] using a 9-parameter registration from the FMRIB's Linear Image Registration Toolbox [10].

We used the cortical reconstruction routine from the Freesurfer software package [11] to segment the pial surface and gray/white matter interfaces, and to generate a tessellation of the resulting surfaces. The software labels a set of 34 cortical subregions per hemisphere, and infers approximate Brodmann areas [12]. We also used Freesurfer to compute the cortical thickness and volume at each vertex over the whole cortex. Thickness was calculated as the average of the distance from the gray matter/cerebrospinal fluid interface to the gray/white matter surface, and vice versa. The volume was defined as the product of the thickness and the area of the surface layer equidistant between the inner and outer cortical surfaces. The area associated with a vertex was defined as the average of the areas of triangles that include that vertex.

Volume values in each individual were filtered using a smoothing kernel of 25 mm full width at half maximum, a value in the range suggested by Lerch and Evans [13] to boost the signal to noise ratio. To remove age and sex-related effects from the analysis, we covaried the thickness and volume measures for effects of age and sex by performing a linear regression (male = 1, female = −1). Covarying for age made no significant difference to the analysis, possibly because the age range of our sample is quite small.

A/C/E model of variance

We estimated relative contributions of additive genetic (A), shared environmental (C), and unique environmental (E) effects on the variance in cortical thickness and volume across the sample of twins. To do so, we used A/C/E structural equation modeling, as outlined in [14], following the implementation described in [8,15].

The observed variable, Z – here the cortical thickness or volume at each vertex for each member of a twin pair – may be modeled as:

$$Z = aA + cC + eE \quad (1)$$

A, C, E are latent variables and a, c, e are the weights of each factor to be determined. The method estimates the vertex-based variance in each of the three free model parameters, constrained by the requirement that $a^2 + c^2 + e^2 = 1$. Measurement and inter-subject registration errors are both classified as part of the E term.

The covariance in the cortical thickness or volume between monozygotic and dizygotic pairs at each vertex was used as an input to the algorithm. The weights were estimated by comparing the covariance matrix implied by the model to the observed sample covariance matrix using maximum-likelihood fitting. The best fitting model was obtained using the Broyden–Fletcher–Goldfarb–Shanno method [16]. We used a permutation distribution to make the results independent of the distribution of the computed statistics [8,15,17].

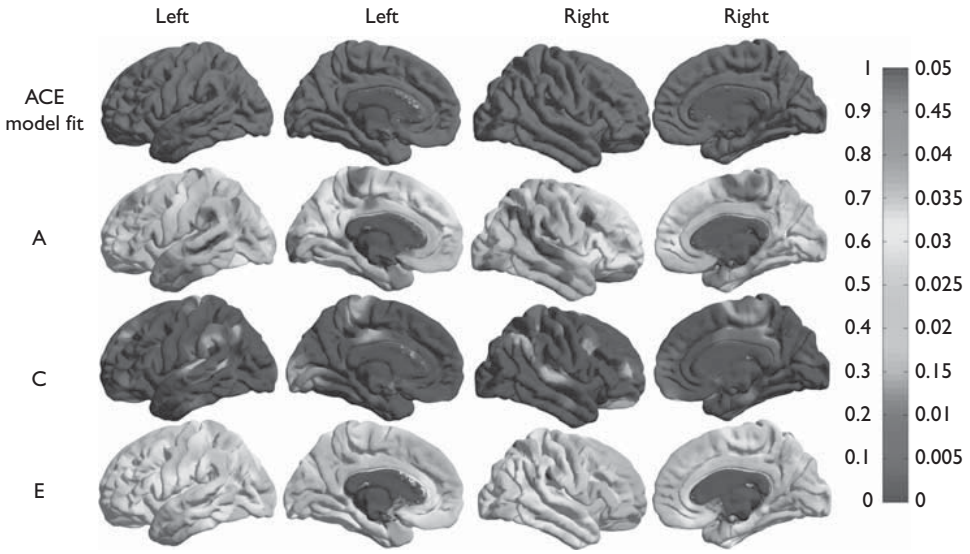
Correlation of full-scale intelligence quotient to thickness

The relationship of full-scale IQ to cortical thickness was assessed at each vertex using a mixed effects regression model to account for similarities within families [8]. Full-scale IQ was added in the model as a fixed effect and a random intercept was included for each family. The analysis was implemented in the *R* statistical package (version 2.9.2) using the 'nlme' library [18]. The nominal P values represent the significance of the full-scale IQ term, as displayed at each vertex in Fig. 3.

Results

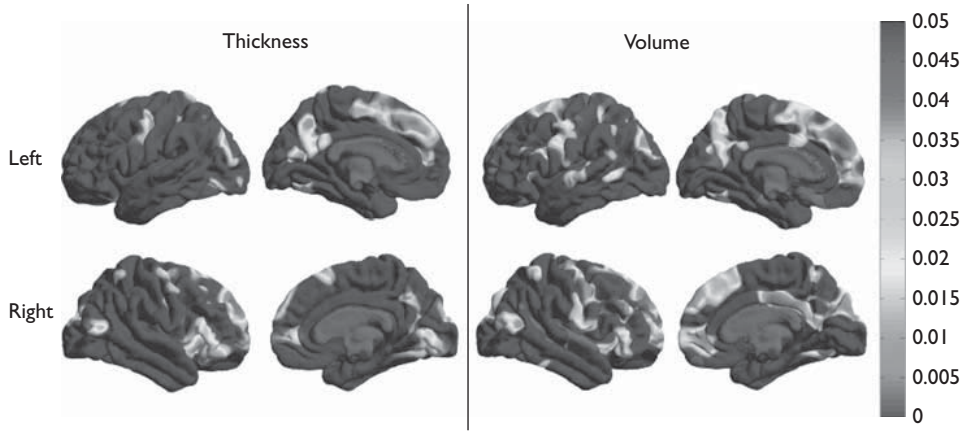
Figure 1 shows detailed cortical surface maps of the additive genetic component (A), common environment (C), and unique environment (E) at each vertex. The P values for the overall A/C/E model fit are also shown. The A/C/E model fits almost everywhere on the cortex except at the corpus callosum (blue patch on the medial side), where thickness or volume measures are not defined. We also considered the reduced A/E model instead of A/C/E. The common environment (C) term was found to improve the fit of the A/C/E model relative to the reduced A/E model, so we only show results for this model here.

Fig. 1



A/C/E analysis of cortical thickness. The two leftmost columns show the sagittal and medial surface of the left hemisphere; the two rightmost ones show the right hemisphere. The color bar shows the color code used in the bottom three rows a^2, c^2, and e^2 on the left, and associated *P* values on the right. Top row: regions are shown (in red), where the A/C/E model fits. Row 2–row 4: maps of the genetic (a^2), combined environmental (c^2), and unique environmental (e^2) contributions to cortical thickness. Figures for cortical volume measures were visually similar and are not shown, but are available upon request.

Fig. 2

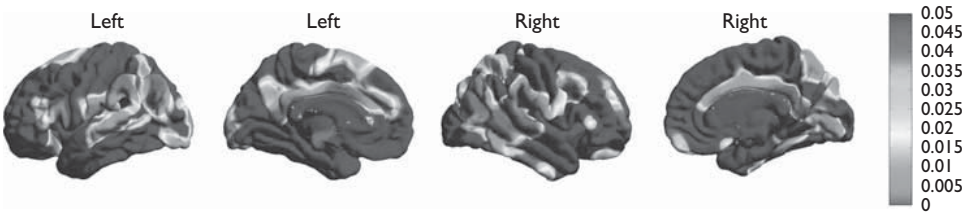


P value associated with the A term, showing the significance of the genetic contribution to brain structure. Thickness is shown on the left panel and cortical volume on the right. The top row shows the left hemisphere and the bottom row shows the right. The color bar displays the *P* values.

P values for the A term are shown in Fig. 2, for both the thickness and volume measures. Areas in the frontal and parietal lobes and the primary visual cortices are significantly genetically influenced. Genetic effects on the cingulate and insula were primarily detected on the left, perhaps owing to hemispheric differences in sulcal patterning in these regions. Lateral temporal regions showed less evidence for heritability.

After computing A/C/E analyses of the cortical measures, we also examined correlations between local cortical thickness and full-scale IQ. Genetic contributions to complex traits such as the full-scale IQ may be studied by assessing the heritability of traits that covary with it (thickness, volume; see Fig. 2) and then computing correlations of the full-scale IQ to that trait, as shown in Fig. 3. Cortical thickness in parietal, medial temporal, occipital and cingulate regions was positively correlated with the full-scale IQ. In addition, cortical thickness in Wernicke's area, the region responsible for language comprehension, showed a significant additive genetic component (A) and was correlated with full-scale IQ.

Fig. 3



Correlation of full-scale intelligence quotient to cortical gray matter thickness, displayed as a nominal *P* value map on the cortex.

Discussion

In this study, we perform a point-wise analysis of cortical measures to determine how they are influenced by genetic versus environmental factors. In earlier large-sample studies [19,20], only a region-wise heritability analysis was performed. Here, we took a somewhat different approach by performing the A/C/E analysis at each cortical surface point. Our results generally agree with those of prior pediatric [4,7] and small-sample adult twin studies [1], which reported significant heritability in frontal, temporal and superior parietal areas. However, although Lenroot *et al.* [4] found significant heritability in the postcentral and supramarginal gyri, here those results were found only as a trend, perhaps because of age differences. *P* values in the study by Winkler *et al.* [19] were generally lower than ours, although statistically significant regions were similar overall.

According to one theory, early-developing regions are more genetically programmed, whereas late-maturing ones tend to be more environmentally influenced. This theory is not supported here, although tensor-based morphometry and diffusion tensor imaging heritability maps have shown evidence for this in subcortical regions [15].

The maps of full-scale IQ correlation with cortical thickness (Fig. 3) and the additive genetic component (A, Fig. 1) shows significant overlap, especially at the Wernicke's areas influencing language.

Our study has some limitations. Although our sample size is large compared with most earlier studies, the confidence intervals of additive genetic (A), common environment (C), and unique environment (E) are still wide. This limits the statistical power to identify differences between our results and earlier findings. Furthermore, impact of test–retest reliability on these results needs to be evaluated, especially in the temporal lobes where thickness measures are prone to MRI-related distortions and susceptibility artifacts. We will address these issues as our sample size continues to increase in this ongoing study.

Highly heritable cortical measures may be useful phenotypes in the search for trait loci that account for differences in human brain structure (see Enigma project [21]). Identifying heritable aspects of brain morphology is an important step towards understanding specific genes that impact brain structure and function and may help in the search for genetic risk factors for a variety of brain disorders [21].

Conclusion

We performed a genetic analysis of cortical thickness and volume in a large sample of twins, by applying the A/C/E structural equation model. The results showed detailed point-wise genetic and environmental contributions on the whole cortex. Several areas in the parietal and frontal lobes were observed to be genetically influenced.

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