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Genetic and environmental influences on cortical thickness among 14-year-old twins

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Abstract

The overall volume of the brain has been found to be under relatively strong genetic control, but the relative strength of genetic and environmental factors on between-person variations in regional cortical thickness in adolescence is still not well understood. Here, we analyzed structural MRI data from 108 14-year-old healthy twins (54 females/54 males) to determine the relative contributions of genes and the environment toward regional variations in gray matter thickness across the cortex. After extracting cortical thickness values at a high spatial resolution, an A/C/E structural equation model that divides the variations into additive genetic (A), shared (C), and unique (E) environmental components was fitted. There was considerable regional variability in the magnitude of genetic influences on cortical thickness after controlling for sex. Regions with genetic contributions of greater than 80% were observed in the prefrontal cortex, predominantly in the bilateral dorsolateral and mesial superior frontal regions. No region showed prominent shared environmental influences, but unique environmental influences of over 80% were found in parietal association regions. The genetic variance for cortical thickness in adolescents in prefrontal regions overlapped with previous findings in adults. However, the unique environmental effects observed in multimodal parietal association cortices with converging inputs from visual, auditory, somatosensory regions, and neighboring secondary association cortices suggest that these regional variations are more shaped by experience and could form targets for early interventions in youth with behavioral disorders.

Keywords

adolescent twins; cortical thickness; heritability; MRI

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Conflicts of interest

There are no conflicts of interest.

Introduction

Twin studies have been invaluable for distinguishing the complex interplay of genetic and environmental influences during development that contribute toward the structural variations in the brain [1,2]. By comparing the correlations between monozygotic (MZ) twins – who are genetically almost identical – and the correlations between dizygotic (DZ) twins, who share approximately half of their segregating genes, with what would be expected under different models of gene action, the relative contribution of genetic and environmental sources toward generating individual differences in brain structure may be estimated. Various methods have been developed to compare the twin correlations between MZ and DZ groups, yielding results that show contributions from both genetic and environmental factors toward variations in the size, shape, and structural complexity of individual brains.

Previous research has focused predominantly on volumetric measures of brain tissue, and has shown that genetic factors account for ~70–90% of the variance in the total cerebral volume and gray and white matter volumes [3,4]. In the few studies that have used an A/C/E model to examine the heritability of brain volumes, shared environmental influences were found to be significant only in the lateral ventricles [3–6]. Compared with brain volumes, very few studies have shown genetic and environmental contributions toward cortical thickness and even fewer have examined the relative contributions at a high spatial resolution [7–10] despite the argument that cortical thickness may be particularly informative for imaging genetics studies in psychiatric and/or neurodevelopmental disorders [11]. Among them, only two studies, to our knowledge, have examined healthy children and adolescents. In one of the studies, Lenroot *et al.* [7] found significant genetic effects on individual differences in cortical thickness in several brain areas, including the dorsal frontal, temporal and orbitofrontal cortices, and superior parietal and inferior temporal cortices bilaterally in a group of healthy children and adolescents. The other study by Yoon *et al.* [8] found significant genetic effects on cortical thickness variation in some overlapping regions that included the middle frontal, inferior frontal, lateral orbitofrontal, occipitotemporal, precentral, parahippocampal gyri, and medial primary somatosensory cortex. In both studies, no significant common environmental influences were found for cortical thickness in any regions and the unique environmental influences were the primary determinants of variance in regions of low heritability including the inferior and superior parietal lobules and the inferior temporal regions.

In this study, we aimed to detail the genetic, shared environmental, and unique environmental contributions of individual differences in cortical thickness across the cortex in a homogeneously aged cohort of 14-year-old young adolescent twins. Well-validated image processing streams implemented with FreeSurfer software [12,13] were used to map 3D profiles of cortical thickness for MZ and DZ twins. A/C/E structural equation models were used to estimate the genetic and environmental effects on the observed variance in cortical thickness. Although there have only been a few related studies in youth and some regional differences have been found in previous findings, we hypothesized that the strongest genetic effects would be observed in the frontal cortex. For environmental effects, we hypothesized that shared environmental influences on cortical thickness would be minimum, whereas unique environmental factors would contribute largely to regions of low heritability such as motor or sensory cortices.

Methods

Participants

The 108 adolescent twins included in this study were recruited from participants of the University of Southern California (USC) Risk Factors for Antisocial Behavior Twin Study

[14]. Participants were included if they (a) indicated willingness to undergo an MRI session during a planned visit for psychological and psychophysiological evaluation, (b) were 14 years of age and without any contraindication to having an MRI scan, and (c) had no history of significant head injury, and no known history of major neurological or psychiatric illness. The twins included 27 DZ pairs (five same-sex male, 10 same-sex female, and 12 opposite-sex twin pairs) and 27 MZ twin pairs (16 male and 11 female twin pairs). Zygosity was established through DNA microsatellite analyses as described previously [15]. Both parents and children provided written informed consent before the study. The study was approved by both the USC and the UCLA Institutional Review Boards.

Magnetic resonance imaging acquisition and preprocessing

All twins were scanned using a 3T Siemens Magnetom Trio whole-body scanner at the USC Dornsife Cognitive Neuroscience Imaging Center. Three-dimensional high-resolution T1-weighted images were acquired using a magnetization-prepared rapid gradient echo protocol with the following parameters: inversion time (TI)/repetition time (TR)/echo time (TE) = 800/2530/3.09 ms, slice thickness = 1 mm without gap, matrix = 256×256 , and field of view = 256×256 mm.

For each participant, cortical thickness was estimated using the FreeSurfer software (Laboratory for Computational Neuroimaging, Martinos Center for Biomedical Imaging, Charlestown, Massachusetts, USA) [12,13] at each vertex over the entire cortex. FreeSurfer processing streams included skull-stripping, tissue segmentation, and spatial normalization of each image volume [16]. To estimate cortical thickness, after intensity normalization, gray–white tissue segmentation was used to extract the pial and gray–white cortical surface. The pial and gray–white cortical surface of each participant was then visually inspected for accuracy and manually corrected if necessary [16]. To boost the signal-to-noise ratio, we applied a 25 mm full-width at half-maximum Gaussian surface-based smoothing kernel to the estimated thickness values [10]. Each participant's cortex was coregistered with the FreeSurfer atlas. To adjust for sex differences, we eliminated the mean differences between boys and girls in the thickness measures by computing residual scores from the linear regression of each cortical thickness for sex (male = 1, female = -1) [10]. Residual scores were then used in the genetic analyses as follows.

Univariate genetic analyses: the A/C/E model

To estimate the relative contribution of additive genetic (A), shared environmental (C), and unique (i.e. unshared) environmental (E) contributions toward the observed variance in cortical thickness measures across the sample, we used structural equation modeling [17], as implemented in several previous studies [10]. Specifically, for each twin, we modeled the thickness value at each vertex as the sum of several latent factors, $Z = aA + cC + eE$, where A , C , and E are latent variables and a , c , and e are the weights of each factor to be determined. The relative contributions toward the overall variance in the observed (thickness) variable, Z , are given by the squared values of these weights – that is $\text{var}(A) = a^2$, $\text{var}(C) = c^2$, and $\text{var}(E) = e^2$ – such that the total variance in cortical thickness is given by $\text{var}(Z) = a^2 + c^2 + e^2$. The method estimates the vertex-based variances for each of the three free model parameters and normalizes the values by constraining the sum of a^2 , c^2 , and e^2 to 1. Measurement errors and interparticipant registration errors are both classified as part of the E term.

The covariance in the cortical thickness between MZ and DZ pairs at each vertex was used as an input to the algorithm [10]. Weights were estimated by comparing the model covariance matrices with the observed sample covariance matrices using maximum-likelihood fitting. The best-fitting model was obtained using the Broyden–Fletcher–

Goldfarb–Shanno method. We used a permutation test to make the inferences robust to the empirical distribution of the computed statistics [10].

Results

Figure 1 shows the vertex-based estimate of genetic and environmental influences on cortical thickness variance, derived from the full A/C/E model. The *P* values for the model fit are also shown. The A/C/E model fits most of the regions across the cortex and was found to be a better fit than the reduced A/E model. Thus, only the results for the full model are shown here. In the left hemisphere, regions with strong genetic contributions of over 80% of variance explained in cortical thickness were observed mostly in the prefrontal cortex, specifically in the superior frontal gyrus, both dorsolaterally and mesially. In the right hemisphere, regions with over 80% of variance explained by genetic effects were observed in the dorsolateral and mesial aspects of the superior frontal gyrus, but in a less prominent pattern compared with the left, as well as the frontal pole, inferior frontal gyrus, posterior supramarginal gyrus, and fusiform gyrus. However, no region was found to show over 80% of variance explained by common environmental influences (i.e. shared by cotwins).

For the unique environmental influence (which also potentially includes measurement error), the effects of over 80% of cortical thickness variance explained were observed in several left hemisphere regions, including the inferior parietal lobule, inferior frontal gyrus, anterior precuneus, postcentral gyrus, and inferior temporal gyrus. In the right hemisphere, unique environmental effects of over 80% variance explained were observed in the superior parietal lobule, anterior cingulate cortex, subgenual mesial frontal cortex, posterior dorsolateral superior frontal gyrus, and the anterior superior section of the insula.

Discussion

Twin imaging studies have been useful for distinguishing the relative contributions of genetic and environmental influences toward between-person variations in brain morphology. In this report, we performed a vertex-based analysis of gray matter thickness across the entire cortex to determine the influence of genetic and environmental factors in a cohort of early adolescent twins across a narrow age window during neurodevelopment.

Supporting our hypothesis, we observed high genetic contributions toward individual differences in frontal cortical thickness, specifically the left dorsolateral and mesial superior frontal gyrus, findings that are consistent with previous reports [10,18]. It has been argued that late-developing regions associated with complex cognitive functions (e.g. the prefrontal cortex) show an increase in the proportion of genetic variance with maturation, which may explain why the relative magnitude of the genetic effect in this region appears to be higher than that found in childhood cohorts, but lower than the heritability found in adult twins in previous studies [9,18]. The finding of greater genetic variation in the left hemisphere than in the right hemisphere is also consistent with previous reports [9,19]. Findings support a strong coupling of variations in brain morphology and genetics [18], particularly in the frontal cortex, which may underlie the high familial liability for some diseases that are associated with frontal cortical thickness (e.g. schizophrenia) [20,21].

Despite the use of the A/C/E model, which allows the separation of familial similarity because of common environmental factors from that because of genetic factors, and the use of a homogeneously aged group, which reduced the environmental variances, we did not find the cortical thickness of any region to show common environmental influences over 80%. The findings are consistent with previous results of children and adolescent cohorts

[8,9], and may suggest a greater importance of genes in the development of the brain, at least with respect to cortical thickness, especially in the frontal cortex. However, our relatively small sample size may not have sufficient power to detect the C effects, especially when they are small [22]. Furthermore, although the ages of the adolescents included were tightly constrained, it is possible that greater variation in brain morphology may have been introduced by using a sample that is close to puberty, with variations in their level and degree of completion of development, perhaps reducing the statistical power.

In terms of unique environmental influences, our study identified the thickness of several brain regions including the superior and inferior parietal lobules to show stronger unique environmental effects. The findings of stronger unique environmental influences on these regions are consistent with previous reports [8,9] and may be supported by functions linked to these regions. For example, the inferior parietal cortex has been implicated in processing spatial attention, topographic information, and language [23]. As such experience is likely to be specific for each individual, and not shared by members of a twin pair, unique environmental factors may be more important in determining individual variations in the cortical thickness of these regions. However, the results should be interpreted with caution as measurement errors that are uncorrelated between the twins also contribute toward the estimation of unique environmental effects.

Conclusion

We performed a genetic analysis of individual differences in cortical thickness in a relatively modest sample size of 108 healthy adolescent twins by applying the A/C/E structural equation methods. Consistent with prior reports, the results indicate genetic effects explaining greater than 80% of between-person variations in cortical thickness in later developing areas associated with higher-order functions such as the dorsal prefrontal cortex. The results further suggest strong unique environmental contributions toward regional cortical thickness variation in the posterior parietal association regions, highlighting the potential for these regions to be shaped more predominantly by differences in personal experience. Future studies with larger samples could help form targets that are better suited for early prevention and interventions in youth with neurodevelopmental and behavioral problems.

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Fig. 1.

The top three rows show estimates of genetic and environmental influence at each vertex for additive genetic (A), common environmental (C), and unique environmental (E) contributions to the variance of cortical thickness between twins. The color bar shows $a^2/c^2/e^2$ values. The bottom row shows the A/C/E model fit, where areas with P -value > 0.05 indicate a good fit in the model (in red).