HHS Public Access

Author manuscript

Proc IEEE Int Symp Biomed Imaging. Author manuscript; available in PMC 2018 December 11.

Published in final edited form as:

Proc IEEE Int Symp Biomed Imaging. 2010 April ; 2010: 101–104. doi:10.1109/ISBI.2010.5490405.

A GENETIC ANALYSIS OF CORTICAL THICKNESS IN 372 TWINS

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Abstract

Imaging genetics is a new field of neuroscience that blends methods from computational anatomy and quantitative genetics to identify genetic influences on brain structure and function. Here we analyzed brain MRI data from 372 young adult twins to identify cortical regions in which gray matter volume is influenced by genetic differences across subjects. Thickness maps, reconstructed from surface models of the cortical gray/white and gray/CSF interfaces, were smoothed with a 25 mm FWHM kernel and automatically parcellated into 34 regions of interest per hemisphere. In structural equation models fitted to volume values at each surface vertex, we computed components of variance due to additive genetic (A), shared (C) and unique (E) environmental factors, and tested their significance. Cortical regions in the vicinity of the perisylvian language cortex, and at the frontal and temporal poles, showed significant additive genetic variance, suggesting that volume measures from these regions may provide quantitative phenotypes to narrow the search for quantitative trait loci that influence brain structure.

Index Terms

brain; image analysis; Magnetic Resonance Imaging; cortex; genetics

1. INTRODUCTION

Brain structure and is influenced by both genetic and environmental factors, and their relative influence varies throughout life, and differs for different brain regions. Many neurological and psychiatric disorders such as Alzheimer's disease, schizophrenia [11] and autism are known to have a genetic component, so it is of great importance to understand which regions of the healthy brain are primarily under genetic influence. In particular, identifying heritable aspects of brain morphology is a step toward understanding which specific genes impact brain structure and function [7], and may in the search for candidate genetic risk factors for brain disorders.

*equal contribution

Twin studies have been used extensively to assess heritability of specific traits, including volumetric brain measures computed from MRI. In general, these studies involve pairs of monozygotic (MZ) and dizygotic twins (DZ); MZ twins share 100% of their genes, but DZ twins share 50% on average, so various methods have compared the two groups and have yielded estimates of the genetic and environmental contributions to various traits, including brain structure.

Here we studied genetic influences on cortical volume, which has been implicated as a promising target for genetic studies. In an early study [22], we computed the heritability of cortical gray matter density in an MRI dataset from 10 MZ and 10 DZ twin pairs. Cortical gray matter measures were under strong genetic control, but to a regionally variable degree, and were correlated with IQ. Posthuma et al. [16] extended earlier work on the heritability of gray matter volumes [1, 21] and used a bivariate genetic analysis to show that common genes were involved in the control of gray and white matter volumes, and IQ, In recent years, with the advent of more computationally efficient automated analysis techniques, data sets comprising hundred of subjects have been collected and analyzed. In [8], the authors assessed genetic, shared environmental, and individual-specific environmental influences on individual differences in the volumes of 96 brain regions of interest (ROIs), in 474 middle-aged male twins (202 pairs; 70 unpaired) from the Vietnam Era Twin Study of Aging (VETSA). They measured thickness of cortical ROIs and the volumes of subcortical ROIs. On average, genetic influences accounted for approximately 70% of the variance in the volume of global, subcortical, and ventricular ROIs and approximately 45% of the variance in the thickness of cortical ROIs. In a related study [15], Panizzon et al. found that total cortical surface area and average cortical thickness were both highly heritable (0.89 and 0.81, respectively) but were essentially unrelated genetically (genetic correlation = 0.08). This suggested that, although cortical volume is a product of thickness and surface area, the resulting measures of volume capture at least two distinct sets of genetic influences. In [10], MRI data from 600 twins (ages 5–19 years old) was used to determine age-related changes in the genetic contribution to brain structure. However, no large-scale study to date has analyzed genetic contributions to cortical volume in healthy adult twins.

Here we set out to study the influence of genetics on cortical volumes in young adult twins (age: 21–27 years) using the A/C/E structural equation model, in a large dataset comprising 194 DZ and 178 MZ twins. This model allows the partitioning of variance into components due to additive genetic (A), shared (C) and unique (E) environmental factors. We hypothesized that genetic influences would be detectable in frontal brain regions, as well as in classical language-related regions where cortical gray matter density has been found to be heritable in prior studies of smaller samples.

2. METHODS

2.1. Data

We collected brain MRI data from a relatively large sample of healthy adult twin subjects, using a 4 Tesla 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 (*MP-RAGE*) sequence to resolve anatomy at high resolution. Acquisition parameters were: inversion time (*TI*)/repetition time (*TR*)/echo time (*TE*) = 1500/2500/3.83 *msec*; flip angle = 15°; slice thickness = 0.9 *mm* with a 256×256×256 acquisition matrix.

2.2. Preprocessing

Images were pre-processed using a cortical reconstruction routine implemented in the Freesurfer software package [4]. The algorithm segments the gray matter/cerebrospinal fluid (GM-CSF) and gray/white matter (GM/WM) interfaces, and generates a tessellation of the resulting surfaces. It then labels a set of 34 cortical subregions per hemisphere, and infers approximate Brodmann areas [5]. We also used Freesurfer to compute the cortical volume at each vertex over the whole cortex (based on the area of the surface layer equidistant between the inner and outer surfaces on the cortical gray matter, and the thickness value computed at each surface vertex). Thickness was calculated as the average of the distance from the GM-CSF to the GM-WM surfaces, and vice versa. Volume values in each individual were filtered using a smoothing kernel of 25 mm FWHM.

2.3. A/C/E model of Variance

We then estimated the relative contributions of additive genetic (A), shared environmental (C) and unique environmental (E) effects on the variance in cortical volume across the sample of twins, in the regions of interest labeled by Freesurfer. To do so, we used structural equation modeling, as outlined in [12], following the implementation described in [9, 3].

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

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

where 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 3 free model parameters, constrained by the requirement that $a^2 + c^2 + e^2 = 1$. Both measurement errors and inter-subject registration errors will be classified as part of the E term.

The covariance in the cortical volume between MZ and DZ pairs at each vertex was used as an input to the path analysis algorithm:

$$Cov(x_1, x_2) = \frac{1}{N_p} \sum_{i=1}^{N_p} (x_1^i - \bar{x})(x_2^i - \bar{x}) \quad (2)$$

where x_1 and x_2 represent the measures for each member of the twin pair, and $\bar{x} = \frac{1}{N_p} \sum_{i=1}^{N_p} x^i$ is the mean of all x^i's, and N_p is the number of twin pairs.

The weights were estimated by comparing the covariance matrix implied by the model to the sample covariance matrix of the observed variables using maximum-likelihood fitting, and

best fitting model is obtained using the Broyden-Fletcher-Goldfarb-Shanno method [17, 13]. To make the results distribution independent, we used permutation methods to obtain the goodness of fit [9, 3, 14].

3. RESULTS

Figure 1 shows a number of parcellated brain regions in which the overall fit of the ACE variance-components model was significant, and where the significance of the additive genetic term (A) was lower than 0.05. These included perisylvian areas in the vicinity of the classical language cortex in the left hemisphere, including the posterior part of the superior temporal gyrus and regions of the inferior parietal cortex. Regions of the orbitofrontal cortex, temporal poles, and frontal poles also displayed significant heritability. In the right hemisphere, significant heritability was detected for regional gray matter volumes in the perisylvian cortex, midsagittal regions of the occipital cortex on the medial wall, and the temporal and frontal poles. Detailed surface-based maps of the cortex were made to show the *p*-values for the ACE model fit, at each point on the cortex. These also emphasized the spatially varying fit of the quantitative genetic models, with significant fits in temporal and frontal poles, and other broadly distributed cortical regions.

4. DISCUSSION

Our results are generally consistent with those in the prior study of pediatric twins [10], which reported significant heritability in frontal, temporal and superior parietal areas. However, while [10] also found significant heritability in the post-central and supramarginal gyri, here those results were not statistically significant. This may be due to the difference in measures used between this and the pediatric study (cortical thickness vs. cortical volume), or to the difference in age of the subjects (children vs. young adults). Further studies will be needed to distinguish between the two factors.

In [9], a multivariate A/C/E analysis was proposed. It would be interesting in the future to apply a multivariate analysis to a set of cortical measures, as it may increase the power of the statistical analysis. Multivariate genetic modeling was also used in [19] to assess the genetic correlation between different cortical ROIs in a large pediatric sample of 600 twins, and in a related study [18] to find genetically mediated intra-cortical associations.

Acknowledgments

This work was generously supported by NIH grant R01 HD050735 and the National Health and Medical Research Council, Australia grant 496682.

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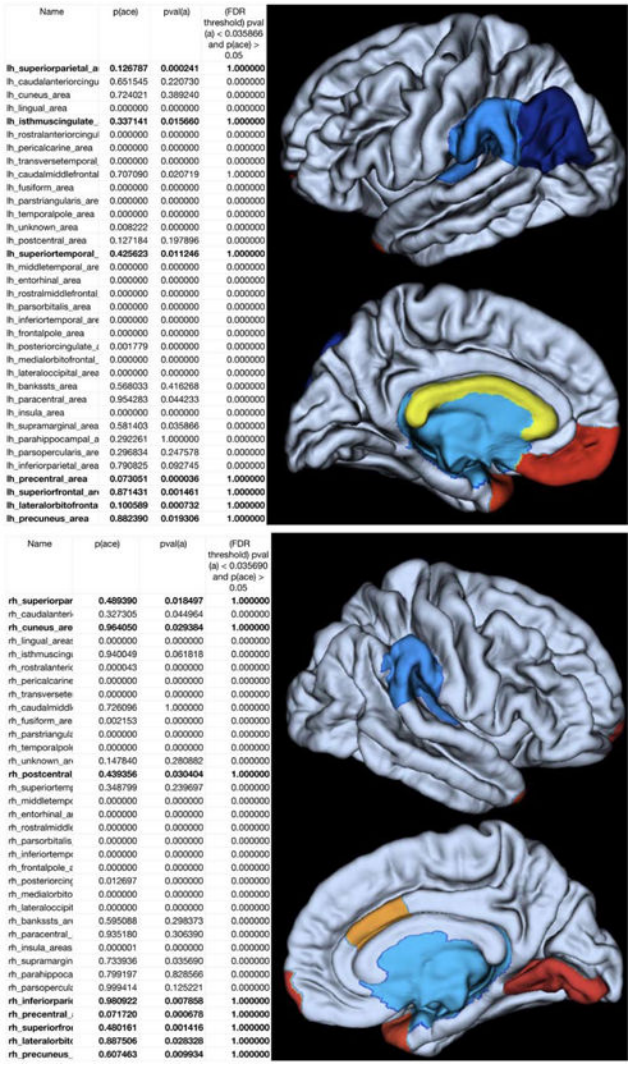

Name	p(ace)	pval(a)	(FDR threshold) pval (a) < 0.035866 and p(ace) > 0.05
lh_superiorparietal_a	0.126787	0.000241	1.000000
lh_caudalanteriorcingu	0.651545	0.220730	0.000000
lh_cuneus_area	0.724021	0.389240	0.000000
lh_lingual_area	0.000000	0.000000	0.000000
lh_isthmuscingulate_	0.337141	0.015660	1.000000
lh_rostralanteriorcingul	0.000000	0.000000	0.000000
lh_pericalcarine_area	0.000000	0.000000	0.000000
lh_transversetemporal_	0.000000	0.000000	0.000000
lh_caudalmiddlefrontal	0.707090	0.020719	1.000000
lh_fusiform_area	0.000000	0.000000	0.000000
lh_parstriangularis_are	0.000000	0.000000	0.000000
lh_temporalpole_area	0.000000	0.000000	0.000000
lh_unknown_area	0.008222	0.000000	0.000000
lh_postcentral_area	0.127184	0.197896	0.000000
lh_superiortemporal_	0.425623	0.011246	1.000000
lh_middletemporal_are	0.000000	0.000000	0.000000
lh_entorhinal_area	0.000000	0.000000	0.000000
lh_rostralmiddlefrontal	0.000000	0.000000	0.000000
lh_parsorbitalis_area	0.000000	0.000000	0.000000
lh_inferiortemporal_are	0.000000	0.000000	0.000000
lh_frontalpole_area	0.000000	0.000000	0.000000
lh_posteriorcingulate_	0.001779	0.000000	0.000000
lh_medialorbitofrontal_	0.000000	0.000000	0.000000
lh_lateraloccipital_area	0.000000	0.000000	0.000000
lh_bankssts_area	0.568033	0.416268	0.000000
lh_paracentral_area	0.954283	0.044233	0.000000
lh_insula_area	0.000000	0.000000	0.000000
lh_supramarginal_area	0.581403	0.035866	0.000000
lh_parahippocampal_a	0.292261	1.000000	0.000000
lh_parsopercularis_are	0.296834	0.247578	0.000000
lh_inferiorparietal_area	0.790825	0.092745	0.000000
lh_precentral_area	0.073051	0.000036	1.000000
lh_superiorfrontal_ar	0.871431	0.001461	1.000000
lh_lateralorbitofronta	0.100589	0.000732	1.000000
lh_precuneus_area	0.882390	0.019306	1.000000

Name	p(ace)	pval(a)	(FDR threshold) pval (a) < 0.035690 and p(ace) > 0.05
rh_superiorpar	0.489390	0.018497	1.000000
rh_caudalanteri	0.327305	0.044964	0.000000
rh_cuneus_are	0.964050	0.029384	1.000000
rh_lingual_area	0.000000	0.000000	0.000000
rh_isthmuscing	0.940049	0.061818	0.000000
rh_rostralanteric	0.000043	0.000000	0.000000
rh_pericalcarine	0.000000	0.000000	0.000000
rh_transversete	0.000000	0.000000	0.000000
rh_caudalmiddl	0.726096	1.000000	0.000000
rh_fusiform_are	0.002153	0.000000	0.000000
rh_parstriangul	0.000000	0.000000	0.000000
rh_temporalpol	0.000000	0.000000	0.000000
rh_unknown_an	0.147840	0.280882	0.000000
rh_postcentral	0.439356	0.030404	1.000000
rh_superiortem	0.348799	0.239697	0.000000
rh_middletempx	0.000000	0.000000	0.000000
rh_entorhinal_a	0.000000	0.000000	0.000000
rh_rostralmiddl	0.000000	0.000000	0.000000
rh_parsorbitalis	0.000000	0.000000	0.000000
rh_inferiortempx	0.000000	0.000000	0.000000
rh_frontalpole_a	0.000000	0.000000	0.000000
rh_posteriorcing	0.012697	0.000000	0.000000
rh_medialorbito	0.000000	0.000000	0.000000
rh_lateraloccipit	0.000000	0.000000	0.000000
rh_bankssts_an	0.595088	0.298373	0.000000
rh_paracentral_	0.935180	0.306390	0.000000
rh_insula_areas	0.000001	0.000000	0.000000
rh_supramargin	0.733936	0.035690	0.000000
rh_parahippoca	0.799197	0.828566	0.000000
rh_parsopercula	0.999414	0.125221	0.000000
rh_inferiorpari	0.980922	0.007858	1.000000
rh_precentral_	0.071720	0.000678	1.000000
rh_superiorfro	0.480161	0.001416	1.000000
rh_lateralorbit	0.887506	0.028328	1.000000
rh_precuneus_	0.607463	0.009934	1.000000

Fig. 1.

Top: Left hemisphere. **Bottom:** Right hemisphere. In both cases, the first column represents the name of the segmented structure; the second column gives the p-value assessing the fit of the ACE quantitative genetic model. In the A/C/E analysis, a high p-value means that the model fits well. The third column gives the p-value for the additive genetic factor (*p*-values below 0.05, uncorrected, show the local statistical significance of the genetic contribution to cortical volume). The fourth column shows a False Discovery Rate (FDR) analysis [2], in which *p*-values for the additive genetic factors are thresholded at a level that controls the expected false discovery rate at 5%. A statistical threshold of p=0.036 can be applied to controls the FDR at 5%. Here, structures that satisfy this threshold have are given a value of 1, and 0 otherwise. Structures highlighted in bold are among those appearing the FDR-corrected map of heritable brain structures. The colors on the maps are arbitrarily chosen to delineate different segmented regions, and do not encode p-value information.

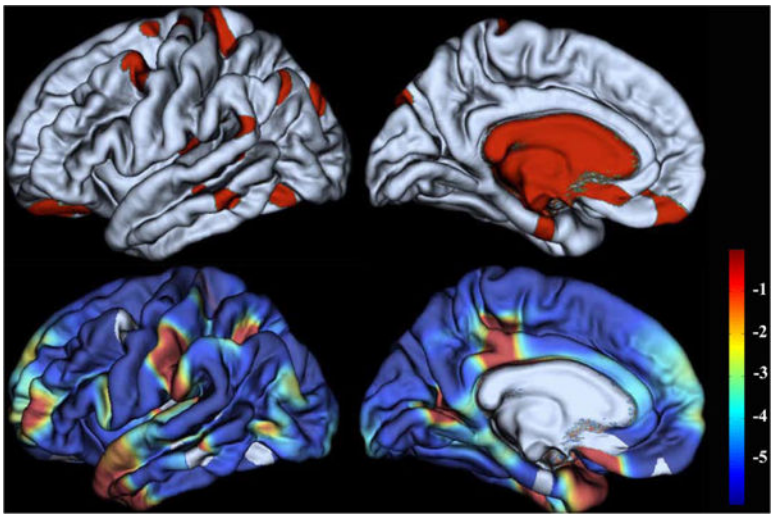

Fig. 2.

Top: Left hemisphere map showing significance values from a regional ACE analysis of cortical volumes. Thickness data were filtered using a smoothing kernel of 25 mm fwhm. **Bottom:** Map of the *p*-values in logarithmic scale showing the regionally varying fit of the ACE model.