Extended Abstract 1 page summary (497/500 words)

Introduction

The cerebral cortex underlies our complex cognitive capabilities. Variations in human cortical surface area and thickness are associated with neurological, psychological and behavioral traits, and can be measured in vivo using magnetic resonance imaging. Studies in model organisms have identified genes influencing cortical structure, but we know little about common genetic variants that influence human cortical structure.

Rationale

To identify genetic variants associated with cortical structure at both the global and regional level, we conducted a genome-wide association meta-analysis of brain magnetic resonance imaging data from 51,665 individuals across 60 sites. We analyzed the surface area and average thickness of the whole cortex and 34 cortical regions with known functional specializations

Results

We identified 369 nominally genome-wide significant loci associated with cortical structure ($P < 5$ x 10^{-8}) in a discovery sample, of 33,992 participants of European ancestry. Of the 360 loci for which replication data were available, 241 loci influencing surface area, and 66 influencing thickness remained significant following replication, with 237 passing multiple testing correction ($P < 8.3$ x 10^{-10}; 187 influencing surface area and 50 influencing thickness).

Common genetic variants explained 34% (SE = 3%) of the variation in total surface area and 26% (SE = 2%) in average thickness; surface area and thickness showed a negative genetic correlation (r_G = -0.32, SE = 0.05, $P = 6.5$ x 10^{-12}) suggesting genetic influences have opposing effects on surface are and thickness. Bioinformatic analyses showed total surface area is influenced by genetic variants that alter gene regulatory activity in neural progenitor cells during fetal development. In contrast, average thickness is influenced by active regulatory elements in adult brain samples, which may reflect processes occurring after mid-fetal development, such as myelination, branching, or pruning. Considered together, these results support the radial unit hypothesis that different developmental mechanisms promote surface area expansion and increases in thickness.
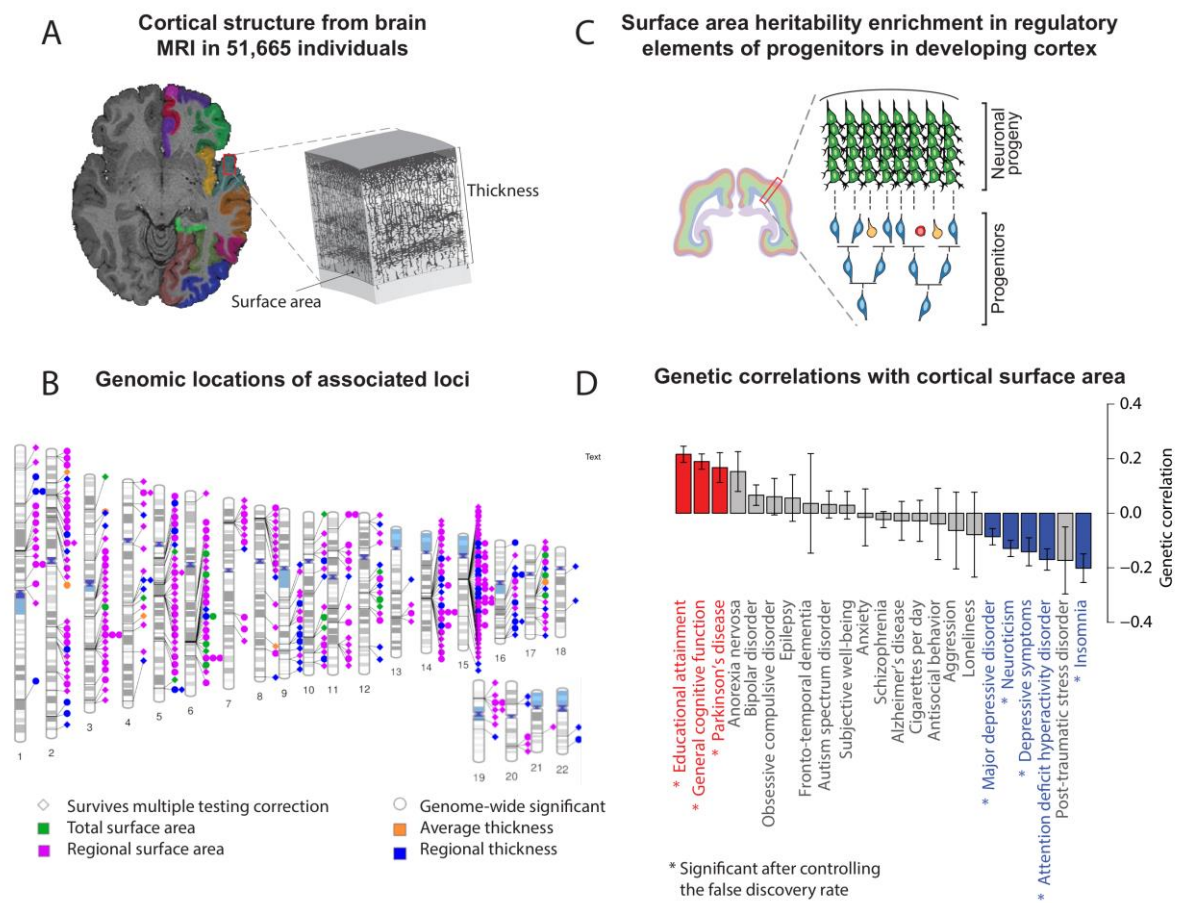
To identify specific genetic influences on individual cortical regions, we controlled for global measures (total surface area or average thickness) in the regional analyses. We identified 175 loci influencing regional surface area, and 46 influencing regional thickness, after multiple testing correction. Loci impacting regional surface area cluster near genes involved in the Wnt signaling pathway, known to influence areal identity.

We observed significant positive genetic correlations and evidence of bidirectional causation of total surface area with both general cognitive functioning, and educational attainment. Additional positive genetic correlations but no evidence of causation was found between total surface area and Parkinson's disease. Negative genetic correlations were evident between total surface area and insomnia, attention deficit hyperactivity disorder, depressive symptoms, major depressive disorder and neuroticism.

Conclusion

This large-scale collaborative work enhances our understanding of the genetic architecture of the human cerebral cortex and its regional patterning. The highly polygenic architecture of the cortex suggests that there are distinct genes involved in the development of specific

cortical areas. Moreover, we find evidence that brain structure is an important phenotype along the causal pathway leading from genetic variation to differences in general cognitive function.

A Cortical structure from brain MRI in 51,665 individuals

Thickness

Surface area

C Surface area heritability enrichment in regulatory elements of progenitors in developing cortex

Neuronal progeny

Progenitors

B Genomic locations of associated loci

◇ Survives multiple testing correction
■ Total surface area (green)
■ Regional surface area (magenta)
○ Genome-wide significant
■ Average thickness (orange)
■ Regional thickness (blue)

D Genetic correlations with cortical surface area

Genetic correlation

* Educational attainment
* General cognitive function
* Parkinson's disease
Anorexia nervosa
Bipolar disorder
Obsessive compulsive disorder
Epilepsy
Fronto-temporal dementia
Autism spectrum disorder
Subjective well-being
Anxiety
Schizophrenia
Alzheimer's disease
Cigarettes per day
Antisocial behavior
Aggression
Loneliness
* Major depressive disorder
* Neuroticism
* Depressive symptoms
* Attention deficit hyperactivity disorder
Post-traumatic stress disorder
* Insomnia

* Significant after controlling the false discovery rate

Figure caption
Identifying genetic influences on human cortical structure. A) Measurement of cortical surface area and thickness from MRI, B) genomic locations of common genetic variants influencing global and regional cortical structure, C) our results support the radial unit hypothesis that the expansion of cortical surface area is driven by proliferating neural progenitor cells, and D) cortical surface area showed genetic correlation with psychiatric and cognitive traits.