

RESEARCH ARTICLE SUMMARY

CORTICAL GENETICS

The genetic architecture of the human cerebral cortex

Katrina L. Grasby*† and Neda Jahanshad*† et al.

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 by magnetic resonance imaging (MRI). Studies in model organisms have identified genes that influence cortical structure, but little is known about common genetic variants that affect human cortical structure.

RATIONALE: To identify genetic variants associated with human cortical structure at both global and regional levels, we conducted a genome-wide association meta-analysis of brain MRI data from 51,665 individuals across 60 cohorts. We analyzed the surface area and

average thickness of the whole cortex and 34 cortical regions with known functional specializations.

RESULTS: We identified 306 nominally genome-wide significant loci ($P < 5 \times 10^{-8}$) associated with cortical structure in a discovery sample of 33,992 participants of European ancestry. Of the 299 loci for which replication data were available, 241 loci influencing surface area and 14 influencing thickness remained significant after replication, with 199 loci passing multiple testing correction ($P < 8.3 \times 10^{-10}$; 187 influencing surface area and 12 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, $P = 6.5 \times 10^{-12}$), which suggests that genetic influences have opposing effects on surface area and thickness. Bioinformatic analyses showed that total surface area is influenced by genetic variants that alter gene regulatory activity in neural progenitor cells during fetal development.

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By contrast, average thickness is influenced by active regulatory elements in adult brain samples, which may reflect processes that occur after mid-fetal development, such as myelination, branching, or pruning.

When 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. After multiple testing correction, we identified 175 loci that influence regional surface area and 10 that influence regional thickness. Loci that affect regional surface area cluster near genes involved in the Wnt signaling pathway, which is 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. We found additional positive genetic correlations between total surface area and Parkinson's disease but did not find evidence of causation. Negative genetic correlations were evident between total surface area and insomnia, attention deficit hyperactivity disorder, depressive symptoms, major depressive disorder, and neuroticism.

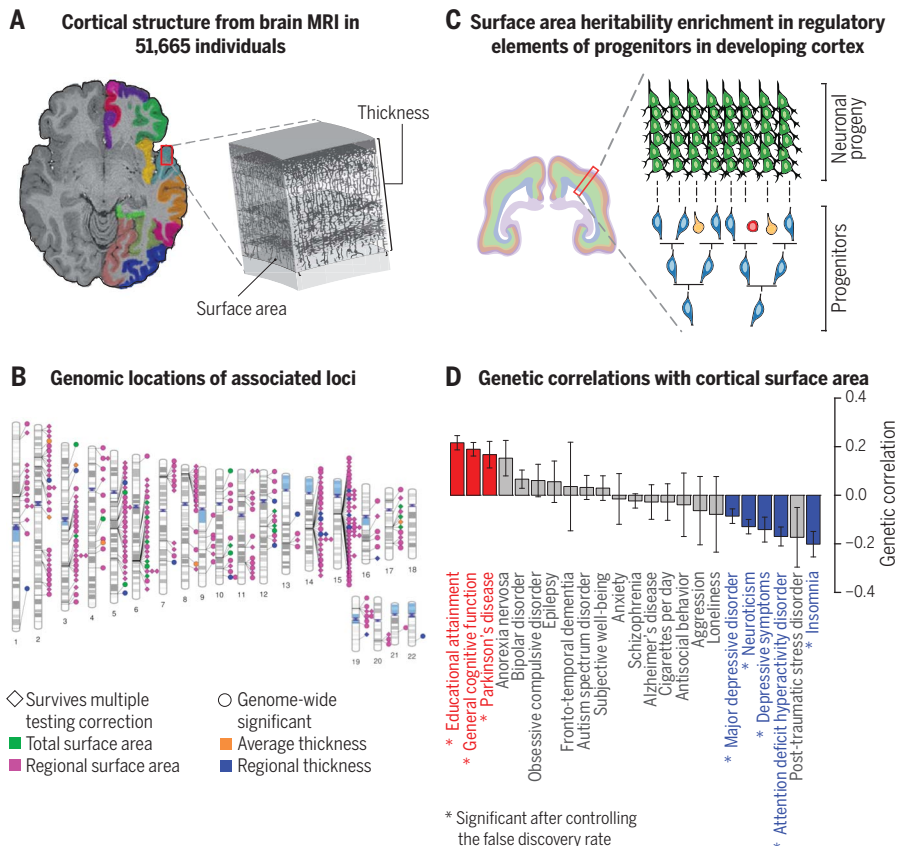
CONCLUSION: This large-scale collaborative work enhances our understanding of the genetic architecture of the human cerebral cortex and its regional patterning. The highly polygenic architecture of the cortex suggests that distinct genes are involved in the development of specific cortical areas. Moreover, we find evidence that brain structure is a key phenotype along the causal pathway that leads from genetic variation to differences in general cognitive function. ■

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Identifying genetic influences on human cortical structure. (A) Measurement of cortical surface area and thickness from MRI. (B) Genomic locations of common genetic variants that influence 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. (D) Cortical surface area shows genetic correlation with psychiatric and cognitive traits. Error bars indicate SE.

RESEARCH ARTICLE

CORTICAL GENETICS

The genetic architecture of the human cerebral cortex

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The cerebral cortex underlies our complex cognitive capabilities, yet little is known about the specific genetic loci that influence human cortical structure. To identify genetic variants that affect cortical structure, we conducted a genome-wide association meta-analysis of brain magnetic resonance imaging data from 51,665 individuals. We analyzed the surface area and average thickness of the whole cortex and 34 regions with known functional specializations. We identified 199 significant loci and found significant enrichment for loci influencing total surface area within regulatory elements that are active during prenatal cortical development, supporting the radial unit hypothesis. Loci that affect regional surface area cluster near genes in Wnt signaling pathways, which influence progenitor expansion and areal identity. Variation in cortical structure is genetically correlated with cognitive function, Parkinson's disease, insomnia, depression, neuroticism, and attention deficit hyperactivity disorder.

The human cerebral cortex is the outer gray matter layer of the brain and is implicated in multiple aspects of higher cognitive function. Its distinctive folding pattern is characterized by convex (gyral) and concave (sulcal) regions. Computational brain mapping approaches use the consistent folding patterns across individual cortices to label brain regions (1). During fetal development, excitatory neurons—the predominant neuronal cell type in the cortex—are generated from neural progenitor cells in the developing germinal zone (2). The radial unit hypothesis (3) posits that the expansion of cortical surface area (SA) is driven by the proliferation of these neural progenitor cells, whereas thickness (TH) is determined by the number of their neurogenic divisions. Variation in global and regional measures of cortical SA and TH have been reliably associated with neuropsychiatric disorders and psychological traits (4) (table S1). Twin and family-based brain imaging studies indicate that SA and TH measurements are highly heritable and are influenced by largely different genetic factors (5–7). Despite extensive studies of genes affecting cortical structure in model organisms, our current understanding of the genetic variation affecting human cortical size and patterning is limited to rare, highly penetrant variants (8, 9). These variants often disrupt cortical development, leading to altered postnatal structure. However, little is known about how common genetic variants influence human cortical SA and TH.

To identify genetic loci associated with variation in the human cortex, we conducted genome-wide association meta-analyses of cortical SA and TH measures in 51,665 individuals, primarily (~94%) of European descent, from 60 cohorts from around the world (tables S2 to S4). Cortical measures were extracted from structural brain magnetic resonance imaging (MRI) scans in 34 regions defined

by the commonly used Desikan-Killiany atlas, which establishes coarse partitions of the cortex. The regional boundaries are based on gyral anatomy labeled from between the depths of the sulci (10, 11). We analyzed two global measures, total SA and average TH, as well as SA and TH for the 34 regions averaged across both hemispheres, yielding 70 distinct phenotypes (Fig. 1A and table S1).

Within each cohort, we used an additive model to conduct a genome-wide association study (GWAS) for each of the 70 phenotypes. To identify genetic influences specific to each region, the primary GWAS of regional measures included the global measure of SA or TH as a covariate. To estimate the multiple testing burden associated with analyzing 70 phenotypes, we used matrix spectral decomposition (12), which yielded 60 independent traits, and a multiple testing significance threshold of $P \leq 8.3 \times 10^{-10}$.

The principal meta-analysis comprised results from 33,992 participants of European ancestry (23,909 from 49 cohorts participating in the ENIGMA consortium and 10,083 from the UK Biobank). We sought replication for loci reaching genome-wide significance ($P \leq 5 \times 10^{-8}$) in an additional ENIGMA cohort (777 participants) and the CHARGE consortium (13) (13,952 participants). In addition, we meta-analyzed eight cohorts of non-European ancestry (2944 participants) to examine the generalization of these effects across ancestries. High genetic correlations were observed between the meta-analyzed ENIGMA European cohorts and the UK Biobank cohort using linkage disequilibrium (LD) score regression (total SA $r_G = 1.00$, z -score $P_{TG} = 2.7 \times 10^{-27}$; average TH $r_G = 0.91$, z -score $P_{TG} = 1.7 \times 10^{-19}$), indicating consistent genetic architecture between the 49 ENIGMA cohorts and data collected from a single scanner at the primary UK Biobank imaging site.

Across the 70 cortical phenotypes, we identified 306 loci that were genome-wide significant in the principal meta-analysis ($P \leq 5 \times 10^{-8}$) (Fig. 1B and table S5). Of these, 118 have not been previously associated with either intracranial volume (ICV) or cortical SA, TH, or volume (13–18). Twenty of these loci were insertions or deletions (INDELs). Eleven INDELs had a proxy single-nucleotide polymorphism (SNP) available in the European replication data; no proxies were available for six INDELs and one SNP. Of the 299 loci for which the SNP or a proxy was available, 255 (SA: 241, TH: 14) remained genome-wide significant when the replication data were included in the meta-analysis, with 199 passing multiple testing correction ($P \leq 8.3 \times 10^{-10}$; SA: 187, TH: 12). Of the 255 loci, 244 were available in the meta-analysis of non-European cohorts. The 95% confidence intervals (CIs) around the non-European meta-analysis effect sizes included those from the European meta-analysis for 241 of these loci. Of the 244 loci available in the non-European cohorts, 189 had effects in the same direction in both the European and non-European meta-analyses, and 111 became more significant when the whole sample was meta-analyzed (table S5 and fig. S1). Variability in effects across ancestry may be due to differences in allele frequency; however, the power for these comparisons is limited, and further comparisons with larger non-European cohorts will help clarify the generalizability of these effects (table S5). We examined gene-based effects (allowing for a 50-kb window around genes) and found significant associations for 253 genes across the 70 cortical phenotypes (table S6). The meta-analytic results are summarized as Manhattan, QQ, Forest, and LocusZoom plots (figs. S2 to S5).

Genetics of total SA and average TH

Common variants explained 34% (SE = 3%) of the variation in total SA and 26% (SE = 2%) in average TH. These estimates account for more than a third of the heritability estimated from the Queensland Twin Imaging cohort (91% for total SA and 64% for average TH) (table S7), indicating that more genetic variants, including rare variants, are yet to be identified. To examine the extent to which our results could predict SA and TH, we derived polygenic risk scores (PRSs) from the principal meta-analysis results. These scores significantly predicted SA and TH in an independent sample of 5095 European participants, explaining between 2 and 3% of the trait variance (given a PRS threshold of $P \leq 0.01$ $R^2_{SA} = 0.029$, linear regression coefficient t test $P = 6.54 \times 10^{-50}$; $R^2_{TH} = 0.022$, t test $P = 3.34 \times 10^{-33}$) (table S8).

We observed a significant negative genetic correlation between total SA and average TH ($r_G = -0.32$, SE = 0.05, z -score $P_{TG} = 6.5 \times 10^{-12}$) (Fig. 2A), which persisted after exclusion of

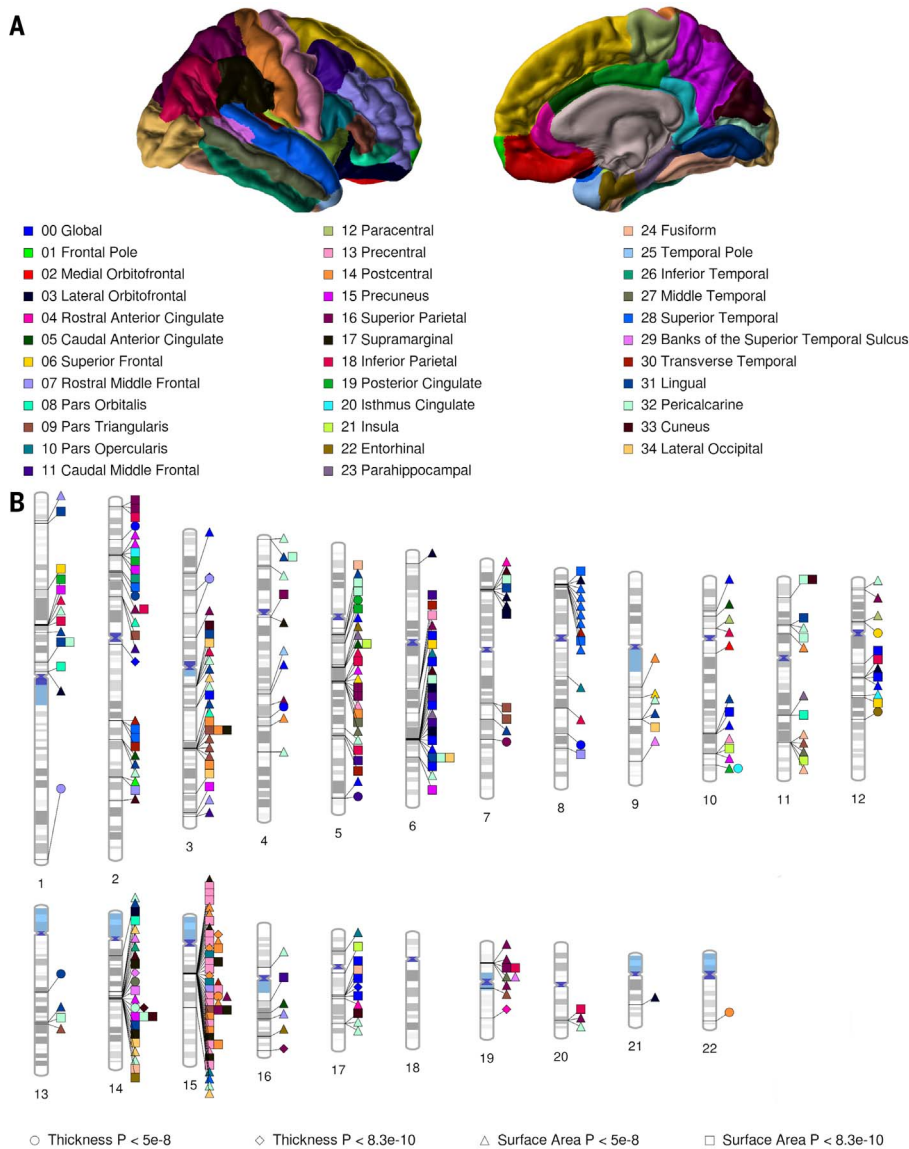


Fig. 1. Regions of the human cortex and associated genetic loci. (A) The 34 cortical regions defined by the Desikan-Killiany atlas. (B) Ideogram of loci that influence cortical SA and TH.

the chromosome 17 inversion region known to influence brain size (14) ($r_G = -0.31$, $SE = 0.05$, $z\text{-score } P_{TG} = 3.3 \times 10^{-12}$). Genetic correlations could indicate causal relationships between traits, pleiotropy, or a genetic mediator influencing both traits. Latent causal variable (LCV) analysis, which tests for causality using genome-wide data (19), showed no evidence of causation [LCV genetic causality proportion (gcp) = 0.06, t test $P_{gcp=0} = 0.729$]. The negative correlation suggests that genetic influences have opposing effects on SA and TH, which may result from pleiotropic effects or genetic effects on a mediating trait that, for example, might constrain total cortical volume. The absence of causality and the small magnitude of this correlation are consistent with the radial unit hypothesis (3), whereby different devel-

opmental mechanisms promote SA expansion and increases in TH.

As expected, total SA showed a positive genetic correlation with ICV. This correlation remained after controlling for height, which demonstrates that this relationship is not solely driven by body size (Fig. 2A and table S8). The global cortical measures did not show significant genetic correlations with the volumes of major subcortical structures (Fig. 2A). The genetic correlation between total SA and the hippocampus is consistent with their shared telencephalic developmental origin.

To identify whether common variation associated with cortical structure relates to gene regulation within a given tissue type, developmental time period, or cell type, we performed partitioned heritability analyses (20) using sets

of gene regulatory annotations from adult and fetal brain tissues (21, 22). Total SA and average TH showed the strongest enrichment of heritability within genomic regions of active gene regulation (promoters and enhancers) in brain tissue and in vitro neural models derived from stem cell differentiation (Fig. 2B and fig. S6A). To examine temporally specific regulatory elements, we selected active regulatory elements that are specifically present in either the mid-fetal brain or the adult cortex. Total SA showed significant enrichment of heritability only within mid-fetal-specific active regulatory elements, whereas average TH showed significant enrichment only within adult-specific active regulatory elements (Fig. 2C and fig. S6B). Stronger enrichment was found in regions of the fetal cortex with more accessible chromatin in the neural progenitor-enriched germinal zone than in the neuron-enriched cortical plate (fig. S6C), similar to a previous analysis for ICV (21). We then performed an additional partitioned heritability enrichment analysis using regulatory elements associated with cell type-specific gene expression derived from a large single-cell RNA sequencing study of the human fetal brain (23). This analysis revealed significant enrichment of total SA heritability in all progenitor cell types, including those in active phases of mitosis as well as three different classes of progenitor cells, including outer radial glia cells, a cell type associated with expansion of cortical SA in human evolution (2) (Fig. 2D and fig. S6D). We also identified significant enrichments in upper layer excitatory neurons, oligodendrocyte progenitor cells, and microglia. These findings suggest that total SA is influenced by common genetic variants that may alter gene regulatory activity in neural progenitor cells during fetal development, supporting the radial unit hypothesis (3). By contrast, the strongest evidence of enrichment for average TH was found in active regulatory elements in the adult brain samples, which may reflect processes that occur after mid-fetal development, such as myelination, branching, or pruning (24).

We conducted pathway analyses to determine whether there was enrichment of association near genes in known biological pathways (25). We found 91 significant gene sets for total SA and 4 significant sets for average TH (table S9). Gene sets associated with total SA included chromatin binding, a process that guides neurodevelopmental fate decisions (26) (table S9 and fig. S7A). In addition, consistent with the partitioned heritability analyses implicating neural progenitor cells in total SA, gene ontology terms relevant to the cell cycle also showed significant enrichment in these analyses.

Loci influencing total SA and average TH

Seventeen of the 255 replicated loci were associated with total SA; 12 survived correction

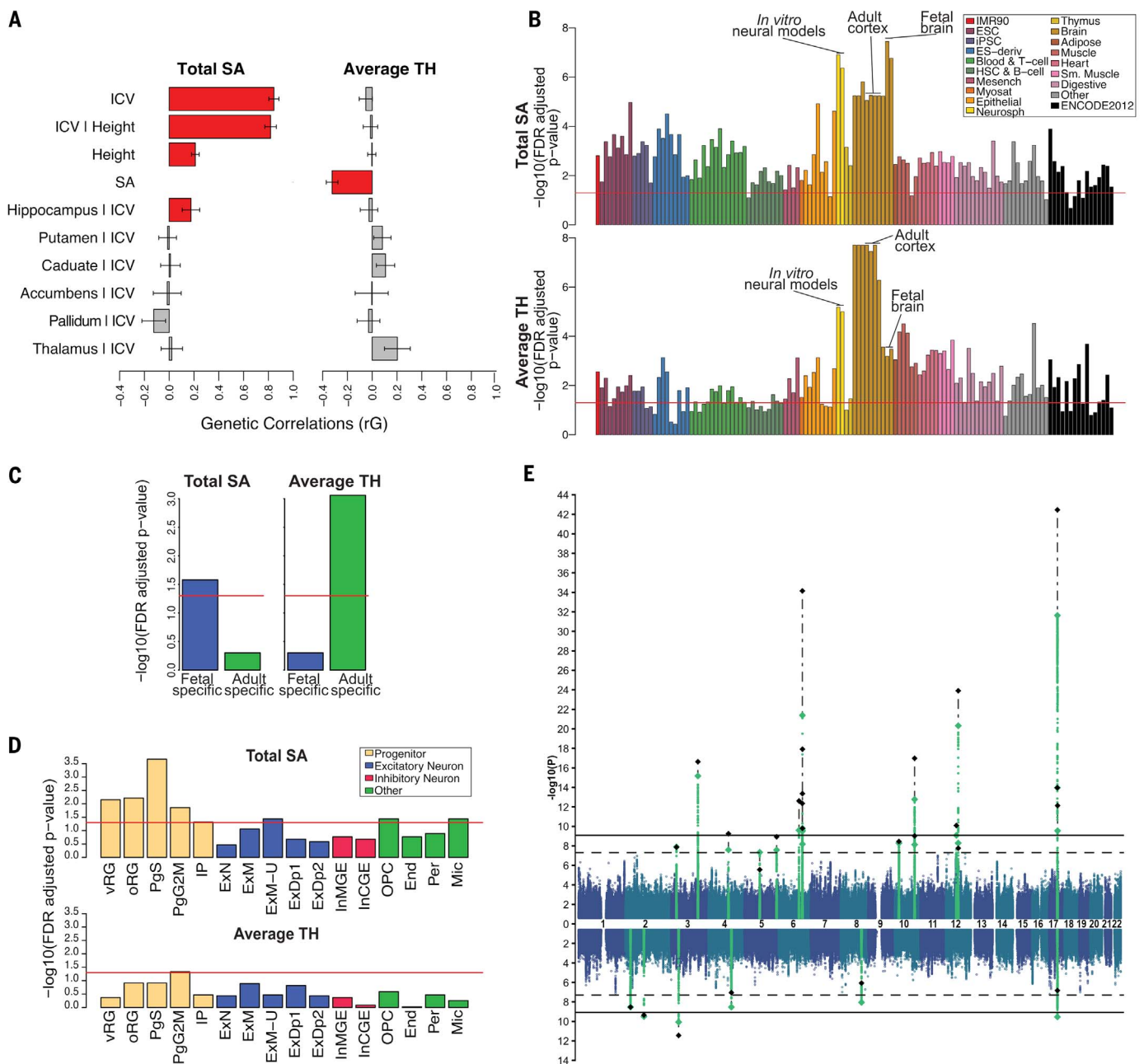


Fig. 2. Genetics of global measures. (A) Genetic correlations between global measures and selected traits (red indicates significant correlation, FDR < 0.05). Error bars indicate SE. (B) Partitioned heritability enrichment in active regulatory elements across tissues and cell types. ESC, embryonic stem cells; iPSC, induced pluripotent stem cells; ES-deriv, embryonic stem derived; HSC, hematopoietic stem cells; Mesench, mesenchymal; Myosat, myosatellite; Neurosph, neurosphere; Sm. Muscle, smooth muscle. (C) Partitioned

heritability enrichment in temporally specific active regulatory elements. (D) Partitioned heritability enrichment in regulatory elements of cell type-specific genes in the fetal brain. (E) Manhattan plot of loci associated with total SA (top) and average TH (bottom). Green diamonds indicate lead SNPs in the principal meta-analysis, black diamonds indicate changes in *P* value after replication, dashed horizontal lines denote genome-wide significance, and solid horizontal lines represent the multiple testing correction threshold.

for multiple testing (Fig. 2E and table S5). Eight loci influencing total SA have been previously associated with ICV (14). These include rs79600142 (principal meta-analysis $P_{MA} = 2.3 \times 10^{-32}$; replication $P_{Rep} = 3.5 \times 10^{-43}$; *P* values reported from all meta-analytic results were for *z*-scores from fixed-effect meta-analyses) in the highly pleiotropic chromo-

some 17q21.31 inversion region, which has been associated with Parkinson's disease (27), educational attainment (28), and neuroticism (29). On 10q24.33, rs1628768 (*z*-score $P_{MA} = 1.7 \times 10^{-13}$; $P_{Rep} = 1.0 \times 10^{-17}$) was shown by our bioinformatic annotations (30) to be an expression quantitative trait locus (eQTL) that influences expression levels of the *INA* gene

and the schizophrenia candidate genes (31) *AS3MT*, *NT5C2*, and *WBP1L* [linear regression coefficient *t* test false discovery rate (FDR)-corrected *P* value for the association of rs1628768 with expression data from surrounding genes $FDR_{CommonMindConsortium(CMC)} < 1.0 \times 10^{-2}$] (tables S11 and S12). This region has been associated with schizophrenia; however,

rs1628768 is in low LD with the schizophrenia-associated SNP rs1191419 ($r^2 = 0.15$) (32). The 6q21 locus influencing total SA is intronic to *FOXO3* (which also showed a significant gene-based association with total SA) (table S6). The major allele of the lead variant rs2802295 is associated with larger total SA (z -score $P_{MA} = 2.5 \times 10^{-10}$; $P_{rep} = 2.5 \times 10^{-13}$) and is in complete LD with rs2490272, a SNP previously associated with higher general cognitive function (33).

One locus not previously associated with ICV is rs1171739 (z -score $P_{MA} = 8.4 \times 10^{-10}$; $P_{rep} = 8.1 \times 10^{-11}$) on 12q13.2. This SNP is in high LD with SNPs associated with educational attainment (28) and is an eQTL for *RPS26* in the fetal (34) and adult cortex (30) [t test of Pearson's r $FDR_{FETAL} = 2.0 \times 10^{-24}$, empirical t test of Pearson's r $FDR_{Genotype-Tissue\ Expression(GTEx)} = 3.3 \times 10^{-40}$] (tables S11 and S12). On 3p24.1, rs12630663 (z -score $P_{MA} = 1.3 \times 10^{-8}$; $P_{rep} = 1.4 \times 10^{-8}$) is of interest because of its proximity (~200 kb) to *EOMES* (also known as *TBR2*), which is expressed specifically in intermediate progenitor cells in the developing fetal cortex (35). rs12630663 is located in a chromosomal region with chromatin accessibility specific to the germinal zone in the human fetal cortex (21). Putatively causal SNPs in this region (table S13) show significant chromatin interactions with the *EOMES* promoter (36). The region also contains many

regulatory elements that, when excised via CRISPR-Cas9 in differentiating neural progenitor cells, significantly reduced *EOMES* expression (21). A rare homozygous chromosomal translocation in the region separating the regulatory elements from *EOMES* (fig. S8) silences *EOMES* expression and causes microcephaly (37), demonstrating that rare and common noncoding variation can have similar phenotypic consequences but to different degrees.

The two replicated loci associated with average TH, neither of which have been previously identified, survived correction for multiple testing (Fig. 2E and table S5). On 3p22.1, rs533577 (z -score $P_{MA} = 8.4 \times 10^{-11}$; $P_{rep} = 3.7 \times 10^{-12}$) is a fetal cortex eQTL (t test $FDR_{FETAL} = 1.8 \times 10^{-4}$) for *RPSA*, encoding a 40S ribosomal protein with a potential role as a laminin receptor (38). Laminins are major constituents of the extracellular matrix and have critical roles in neurogenesis, neuronal differentiation, and migration (39). On 2q11.2, rs11692435 (z -score $P_{MA} = 3.2 \times 10^{-10}$; $P_{rep} = 4.5 \times 10^{-10}$) encodes a missense variant (p.A143V) predicted to affect *ACTR1B* protein function (40) and is an *ACTR1B* eQTL in the fetal cortex (t test $FDR_{FETAL} = 3.9 \times 10^{-2}$) (tables S11 and S12). *ACTR1B* is a subunit of the dynactin complex involved in microtubule remodeling, which is important for neuronal migration (41).

Genetics of regional SA and TH

The amount of phenotypic variance explained by common variants was higher for SA (8 to 31%) than TH (1 to 13%) for each of the specific cortical regions (Fig. 3, A and B, and table S7). To focus on region-specific influences, we controlled for global measures in the regional GWAS, which reduced the covariance between the regional measures (tables S14 and S15). Similar to the genetic correlation between global SA and TH, when significant, genetic correlations between regional SA and TH within the same region were moderate and negative (tables S14 and S15). This suggests that genetic variants that contribute to the expansion of SA in a specific region tend to also contribute to thinner TH in that region.

Genetic correlations between regions were calculated separately for SA and TH. Most genetic correlations between regions did not survive multiple testing correction. For SA, significant positive genetic correlations were generally found between physically adjacent regions and negative correlations between more distal regions (Fig. 3A). This pattern mirrored the phenotypic correlations between regions and was also observed for TH (Fig. 3, A and B). Consistent with this finding, hierarchical clustering of the genetic correlations resulted in a general grouping by physical proximity (fig. S9). These positive genetic

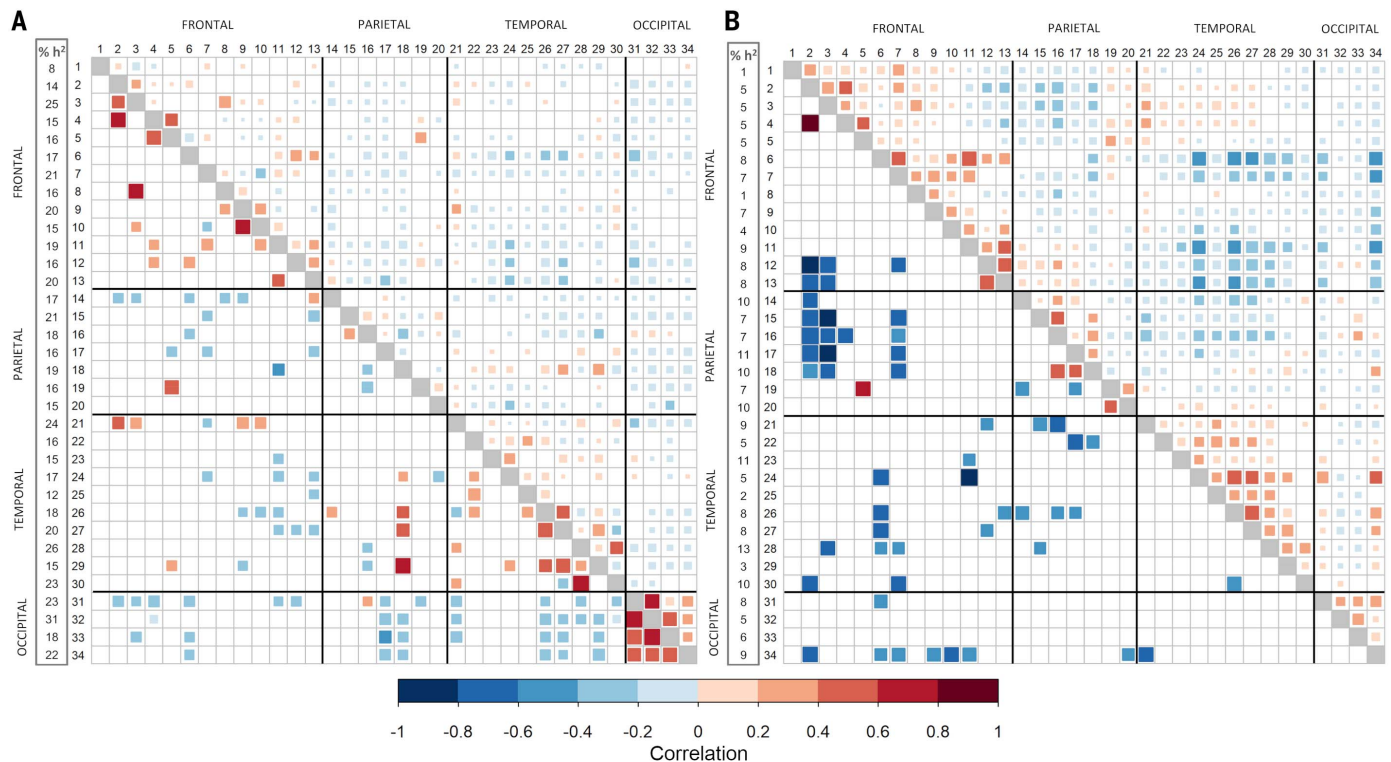


Fig. 3. Genetic and phenotypic correlations between cortical regions. (A) Surface area. (B) Thickness. Regions are numbered according to the inset key of Fig. 1A. The proportion of variance accounted for by common genetic variants is shown in the first column (h^2_{SNP}). Phenotypic correlations from the UK Biobank are in the upper right triangle. Genetic correlations from the principal meta-analysis are in the lower left triangle. Only significant correlations are shown.

correlations were strongest between SA of regions surrounding the major, early-forming sulci (e.g., the pericalcarine, lingual, cuneus, and lateral occipital regions surrounding the calcarine sulcus), which may reflect genetic effects acting on the development of the sulci (11).

To further investigate biological pathways that influence areal (regional) identity, we used multivariate GWAS analyses (42) to aggregate association statistics separately for regional SA and TH. These analyses identify variants shared across regions and those within specific regions while accounting for the phenotypic correlations between regions. Pathway analyses of the multivariate SA results showed significant enrichment for 903 gene sets (table S10), many of which are involved in Wnt signaling, with the canonical Wnt signaling pathway showing the strongest enrichment (z -score, $P = 8.8 \times 10^{-11}$). Wnt proteins regulate neural progenitor fate decisions (43, 44) and are expressed in spatially specific manners that influence areal identity (45). Pathway analyses of the multivariate TH results did not yield any findings that survived multiple testing correction.

Loci influencing regional SA and TH

A total of 224 loci were nominally associated with regional SA and 12 with regional TH; of these, 175 SA and 10 TH loci survived multiple testing correction (table S5). As shown in Fig. 1B, most loci were associated with a single cortical region. Of the loci influencing regional measures, a few were also associated with global measures. Those that were associated showed effects in the same direction, indicating that the significant regional loci were not due to collider bias (46) (fig. S10).

The strongest regional association was observed on chromosome 15q14 with the precentral SA (rs1080066, z -score $P_{MA} = 1.8 \times 10^{-137}$; $P_{rep} = 4.6 \times 10^{-189}$; variance explained = 1.03%) (Fig. 4A). Across 11 traits, we observed 41 independent significant associations from 18 LD blocks (r^2 threshold ≤ 0.02) (Fig. 4B and table S5). As we observed strong association with the SA of both pre- and post-central gyri (Fig. 4C), we localized the association within the central sulcus in 5993 unrelated individuals from the UK Biobank. The most significant association between rs1080066 and sulcal depth was observed around the pli de passage fronto-pariétal moyen (linear regression coefficient t test $P = 7.9 \times 10^{-21}$), a region associated with hand fine-motor function in humans (47), which shows distinctive depth patterns across different species of primates (48) (Fig. 4D). rs1080066 is a fetal cortex eQTL for a downstream gene, *EIF2AK4* (t test $FDR_{FETAL} = 4.8 \times 10^{-2}$), that encodes the GCN2 protein, which is a negative regulator of synaptic plasticity, memory, and neurogenesis (49). The func-

tional data also highlight *THBS1* via chromatin interaction between the rs1080066 region and the promoter in neural progenitor cells and an eQTL effect in whole blood (z -score $FDR_{BIOS_{genelevel}} = 6.1 \times 10^{-6}$). *THBS1* has roles in synaptogenesis and the maintenance of synaptic integrity (50).

Consistent with enrichment in the pathway analyses, many other loci were located in regions with functional links to genes involved in Wnt signaling (fig. S7B), including 1p13.2, where rs2999158 (lingual SA, z -score $P_{MA} = 1.9 \times 10^{-11}$; $P_{rep} = 3.0 \times 10^{-11}$; pericalcarine SA, z -score $P_{MA} = 1.9 \times 10^{-11}$; $P_{rep} = 9.9 \times 10^{-16}$) is an eQTL for *ST7L* and *WNT2B* (t test $FDR_{CMC} < 1.0 \times 10^{-2}$) in the adult cortex (tables S11 and S12). On 14q23.1, we observed 20 significant loci (table S5) from four LD blocks. The strongest association here was for the precuneus SA (rs73313052: z -score $P_{MA} = 1.1 \times 10^{-24}$; $P_{rep} = 2.2 \times 10^{-35}$). These loci are located near *DACT1* and *DAAMI*, both of which are involved in synapse formation and are key members of the Wnt signaling cascade (51, 52). rs73313052 and high-LD proxies are eQTLs for *DAAMI* (t test $FDR_{CMC} < 1.0 \times 10^{-2}$) in the adult cortex (tables S11 and S12).

Several of our regional associations occur near genes with known roles in brain development. For example, on chromosome 1p22.2, rs1413536 (associated with the inferior parietal SA: z -score $P_{MA} = 1.6 \times 10^{-10}$; $P_{rep} = 3.1 \times 10^{-14}$) is an eQTL in the adult cortex for *LMO4* (t test $FDR_{CMC} < 1.0 \times 10^{-2}$), with chromatin interactions between the region housing both this SNP and rs59373415 (associated with the precuneus SA: z -score $P_{MA} = 1.6 \times 10^{-10}$; $P_{rep} = 5.3 \times 10^{-12}$) and the *LMO4* promoter in neural progenitor cells (tables S11 and S12). *Lmo4* is one of the few genes already known to be involved in areal identity specification in the mammalian brain (53).

Genetic relationships with other traits

To examine shared genetic effects between cortical structure and other traits, we performed genetic correlation analyses with GWAS summary statistics from 23 selected traits. We observed significant positive genetic correlations between total SA and general cognitive function (54), educational attainment (28), and Parkinson's disease (27), indicating that allelic influences resulting in larger total SA are, in part, shared with those influencing greater cognitive capabilities as well as increased risk for Parkinson's disease. For total SA, significant negative genetic correlations were detected with insomnia (55), attention deficit hyperactivity disorder (ADHD) (56), depressive symptoms (57), major depressive disorder (58), and neuroticism (29) (Fig. 5A and table S16), again indicating that allelic influences resulting in smaller total SA are partly shared with those influencing an increased risk for these dis-

orders and traits. To map the magnitude of these effects across the brain, we calculated genetic correlations across cortical regions without correction for the global measures (Fig. 5B). Genetic correlations with average TH did not survive multiple testing correction, perhaps owing to the weaker genetic associations detected in the TH analyses. At the regional level, significant genetic correlations were observed between precentral TH and general cognitive function ($r_G = 0.27$, z -score $P_{rG} = 2.5 \times 10^{-5}$) and educational attainment ($r_G = 0.25$, z -score $P_{rG} = 4.0 \times 10^{-4}$), as well as between the inferior parietal TH and educational attainment ($r_G = -0.19$, z -score $P_{rG} = 5.0 \times 10^{-4}$). To confirm that these correlations were not driven by the presence of cases within the meta-analysis, genetic correlations were recalculated from a meta-analysis of GWAS from population-based cohorts and GWAS of controls from the case-control cohorts ($N = 28,503$ individuals). All genetic correlations remained significant, with the exception of the genetic correlation between total SA and depressive symptoms (table S17).

We performed bidirectional Mendelian randomization (MR) (59) and LCV (19) analyses to investigate potential causal relationships underlying the observed genetic correlations with total SA. Both methods provided evidence of a causal effect of total SA on general cognitive function (inverse variance-weighted MR $b_{MR-IVW} = 0.15$, SE = 0.01, z -score $P = 4.6 \times 10^{-8}$; LCV $gcp = 0.40$, 95% CIs: 0.23 to 0.57, t test $P_{gcp=0} = 1.4 \times 10^{-9}$) and educational attainment ($b_{MR-IVW} = 0.12$, SE = 0.01, z -score $P = 2.1 \times 10^{-21}$, $gcp = 0.49$, 95% CIs: 0.26 to 0.72, t test $P_{gcp=0} = 8.0 \times 10^{-9}$) (tables S18 and S19). The MR analyses also indicated association in the reverse direction for both general cognitive function and educational attainment (table S18); however, this was not supported by the LCV analyses (table S19). We found limited to no support for a causal relationship in either direction between total SA and the six other traits that showed significant genetic correlations (tables S18 and S19). Taken together, these findings suggest that the previously reported phenotypic relationships between cortical SA and general cognitive function (60, 61) may partly reflect underlying causal processes.

Discussion

Here we present a large-scale collaborative investigation of the effects of common genetic variation on human cortical structure using data from 51,665 individuals from 60 cohorts. Current knowledge of genes that affect cortical structure has been derived largely from creating mutations in model systems, such as the mouse, and observing effects on brain structure (8). Given the differences between mouse and human cortical structures (62), this study

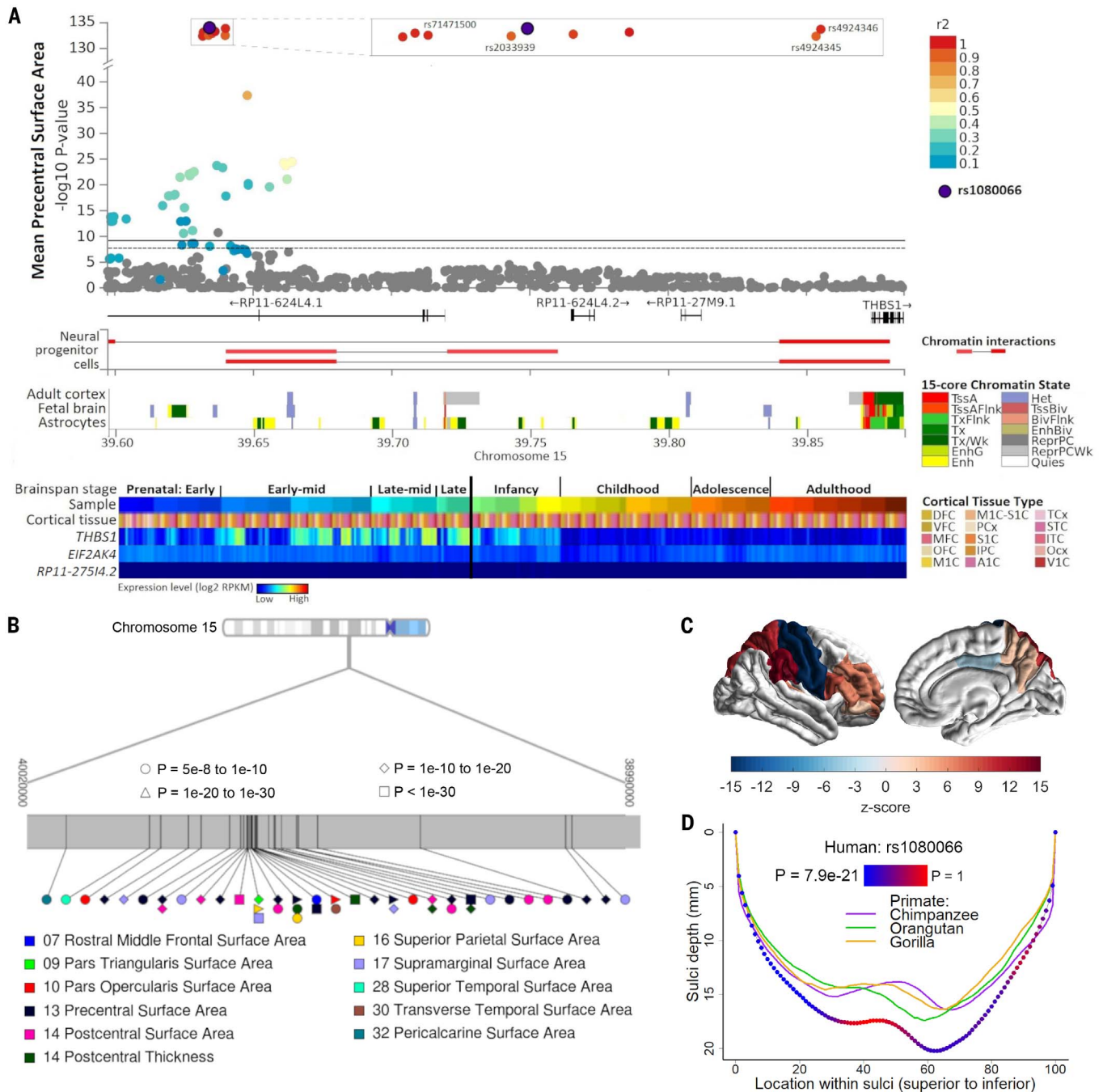


Fig. 4. Genetics of regional measures. (A) Regional plot for rs1080066, including additional lead SNPs within the LD block and surrounding genes, chromatin interactions in neural progenitor cells, chromatin state in RoadMap brain tissues, and BRAINSPAN candidate gene expression in brain tissue. (B) Ideogram of 15q14, detailing the significant independent loci and cortical regions. (C) rs1080066 (G allele) association with SA of regions. (D) rs1080066 association with central sulcus depth and depth of several primate species. RoadMap chromatin states: TssA, active transcription start site (TSS); TssAFlnk, flanking active TSS; TxFlnk, transcription at gene 5' and 3'; Tx, strong transcription; TxWk, weak transcription; EnhG, genetic

enhancers; Enh, enhancers; Het, heterochromatin; TssBiv, bivalent/poised TSS; BivFlnk, flanking bivalent TSS/enhancer; EnhBiv, bivalent enhancer; ReprPC, repressed Polycomb; ReprPCWk, weak repressed Polycomb; Quies, quiescent/low. BRAINSPAN cortical tissue types: DFC, dorsolateral prefrontal cortex; VFC, ventrolateral prefrontal cortex; MFC, anterior cingulate cortex; OFC, orbital frontal cortex; MIC, primary motor cortex; MIC-S1C, primary motor-sensory cortex; PCx, parietal neocortex; S1C, primary somatosensory cortex; IPC, posteroventral parietal cortex; A1C, primary auditory cortex; TCx, temporal neocortex; STC, posterior superior temporal cortex; ITC, inferolateral temporal cortex; Ocx, occipital neocortex; VIC, primary visual cortex.

provides genome-wide insight into human variation and genes that influence a characteristically human phenotype. Previous studies have identified rare variants that

have substantial effects on cortical structure in humans (8), and this study adds to the catalog of the type of variation that affects human cortical structure.

We show that the genetic architecture of the cortex is highly polygenic and that variants often have a specific effect on individual cortical regions. This finding suggests that there

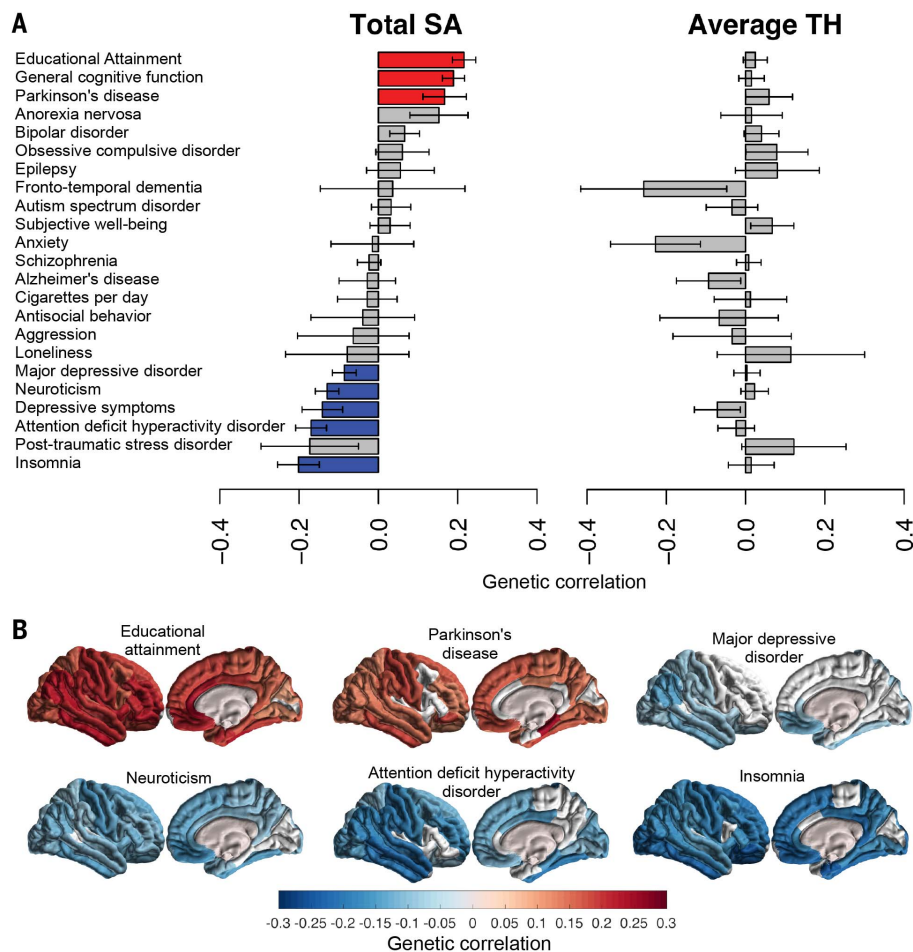


Fig. 5. Genetic correlations with neuropsychiatric and psychological traits. (A) Genetic correlations with total SA and average TH. Significant positive correlations are shown in red; significant negative correlations are shown in blue. Error bars indicate SE. (B) Regional variation in the strength of genetic correlations between regional SA (without correction for total SA) and traits showing significant genetic correlations with total SA.

are distinct genes involved in the development of specific cortical areas and raises the possibility of developmental and regional specificity in eQTL effects. We also find that rare variants and common variants in similar locations in the genome can lead to similar effects on brain structure, albeit to different degrees. For example, a balanced chromosomal translocation near *EOMES* leads to microcephaly in a region abutting a common variant signal associated with small changes in cortical SA (fig. S8).

We provide evidence that genetic variation affecting gene regulation in progenitor cell types, present in fetal development, affects adult cortical SA. This is consistent with the radial unit hypothesis, which states that an increase in proliferative divisions of neural progenitor cells leads to an expansion of the pool of progenitors, resulting in increases in neuronal production and cortical SA (3, 62). Notably, we see an enrichment of heritability in cortical SA within regulatory elements that influence outer radial glia cells, a cell type that

is considerably more prevalent in gyrencephalic species such as humans and has been hypothesized to account for the increased progenitor pool size in humans (2).

We also find that Wnt signaling genes influence areal expansion in humans, as previously reported in model organisms such as mice (45). Cortical TH was associated with loci near genes implicated in cell differentiation, migration, adhesion, and myelination. Consequently, molecular studies in the appropriate tissues, such as neural progenitor cells and their differentiated neurons, will be critical for mapping the involvement of specific genes.

We demonstrate that genetic variation associated with brain structure also affects general cognitive function, Parkinson's disease, depression, neuroticism, ADHD, and insomnia. This implies that the genetic variants that influence brain structure also shape brain function. Although most of the differences in cortical structure observed in these disorders have been reported for TH, our results show significant

genetic correlations for SA, perhaps suggesting that the phenotypic differences observed in cortical TH (table S1) partially reflect environmental influences or effects of illness or treatment. We find evidence that brain structure is a key phenotype along the causal pathway that leads from genetic variation to differences in general cognitive function and educational attainment.

In summary, this work identifies genome-wide significant loci associated with cortical SA and TH and enables a deeper understanding of the genetic architecture of the human cerebral cortex and its patterning.

Materials and methods summary

Participants

Participants were genotyped individuals, with cortical MRI data, from 60 cohorts. Participants in all cohorts gave written informed consent, and each site obtained approval from local research ethics committees or institutional review boards. Ethics approval for the meta-analysis was granted by the QIMR Berghofer Medical Research Institute Human Research Ethics Committee (approval: P2204).

Imaging

Measures of cortical SA and TH were derived from in vivo whole-brain T1-weighted MRI scans using FreeSurfer MRI-processing software (7). SA and TH were quantified for each individual across the whole cortex and within 34 distinct gyral-defined regions, according to the Desikan-Killiany atlas. The regions were averaged across both hemispheres (10).

Genetic association analyses

Within each cohort, GWASs were conducted on each of the 70 imaging phenotypes. After quality control, these data were meta-analyzed using METAL (63). Initially the GWASs from European cohorts were meta-analyzed together, yielding the principal results that were used in all subsequent analyses. We sought replication of the genome-wide significant loci with data from the CHARGE Consortium. To examine generalization of effects, the GWASs from the non-European cohorts were meta-analyzed together, and we then collectively meta-analyzed the European and non-European results. Polygenic risk scores were derived from the principal meta-analysis and used to predict the amount of variance explained by the association of common genetic variants with the cortical SA and TH in an independent sample.

SNP heritability and tests for genetic correlations and causation

Heritability explained by common genetic variants (SNP heritability) was estimated using LD score regression (64). Genetic correlations between cortical regions were estimated using cross-trait LD score regression

(65). To examine genetic relationships with other traits, we estimated genetic correlations using cross-trait LD score regression. To determine whether these correlations were causal, we used MR (59) and LCV analyses (19).

Partitioned heritability

Partitioned heritability analysis was used to estimate the percentage of heritability explained by annotated regions of the genome (66). Heritability enrichment was first estimated in active regulatory elements across tissues and cell types (21, 22). Subsequently, heritability enrichment was estimated in mid-fetal-specific active regulatory elements and adult cortex-specific active regulatory elements. Finally, heritability enrichment was estimated in regulatory elements of cell type-specific genes in the fetal brain (23).

Functional follow-up

After obtaining the principal meta-analytic results, we followed up with gene-based association analysis using MAGMA (67). A multivariate analysis of the regional association results was conducted using TATES (42). Pathway analyses were conducted on the global measures and the results from the multivariate analyses using DEPICT to identify enrichment of association in known genetic functional pathways (25). To identify putatively causal variants, we performed fine-mapping with CAVIAR (68). Potential functional impact was investigated using FUMA (30), which annotates the SNP location, nearby enhancers or promoters, chromatin state, associated eQTLs, and the potential for functional effects through predicted effects.

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SUPPLEMENTARY MATERIALS

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Materials and Methods

Supplementary Text

Consortium Authors

Additional Cohort Information

Supplementary Acknowledgments

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