

## Supplementary Materials for

### The genetic architecture of the human cerebral cortex

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**Other Supplementary Material for this manuscript includes the following:**

(available at [science.sciencemag.org/content/367/6484/eaay6690/suppl/DC1](https://science.sciencemag.org/content/367/6484/eaay6690/suppl/DC1))

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## Materials and Methods

### Imaging

Measures of cortical surface area (SA) and thickness (TH) were derived from *in vivo* whole brain T1-weighted magnetic resonance imaging (MRI) scans using FreeSurfer MRI processing software (1) (table S3). SA and TH were quantified for each subject within 34 distinct gyral-defined regions in each brain hemisphere according to the Desikan-Killiany atlas (10) (Fig. 1A). SA was measured at the grey-white matter boundary. TH was measured as the average distance between the white matter and pial surfaces. The total SA and average TH of each hemisphere was computed separately. High test-retest correlations have been previously reported for all measures with the exception of the frontal and temporal poles (7). Image processing and quality control were implemented at the cohort level following detailed, harmonized protocols.

Site analysts visually inspected the 34 bilateral cortical Desikan-Killiany atlas segmentations for each subject. Visual inspection was conducted to assess extraction of the cortical grey matter ribbon, to identify regional boundary errors on the cortical surface, and ensure the accuracy of anatomical labels. Inspection was slice by slice on an orthogonal view, as well as on the external surface view. Regions marked as “failed segmentations” were excluded from analyses. SA and TH estimates beyond 2.698 SD from the mean were flagged in order to be more carefully inspected by the respective site analysts. A quantitative assessment of quality was not applied; subjects or regions were marked either as acceptable or not by a human rater. As this was a binary “pass” or “fail” flag for each region, no additional metrics were added to the statistical analysis at the site level. For sites that removed subjects for only the region that failed, the number of subjects available varied across regions. For sites that removed subjects entirely for regional fails, the total number of subjects available was the same as for all regions. We also note that some cohorts removed poor quality scans from their database, so for some cohorts the number of quality control issues may be limited. We include the percent of regional data available at the cohort-level in table S3. The protocols that were used for the imaging quality control are available online from the ENIGMA website (<http://enigma.ini.usc.edu/protocols/imaging-protocols>).

Phenotype distributions for all traits in all cohorts were inspected centrally prior to meta-analysis (fig. S11). Any cohort where the phenotypic distribution for a given trait showed deviation from expectations that could not be resolved through re-analysis or outlier inspection were excluded from analyses of that trait.

### Genome-wide association analyses

At each site, genotypes were imputed using either the 1000 Genomes Project (70) or Haplotype Reference Consortium (71) references (table S4). To ensure consistency in the correction for ancestry and stability of the correction given the relatively small sample sizes, each cohort also ran the same multidimensional scaling (MDS) analysis protocol in which the data from the HapMap 3 populations were merged with the site level data and MDS components were calculated across this combined data set. Within each cohort, genome-wide association (GWAS) was conducted using an additive model including covariates to control for the effects of age, age<sup>2</sup>, sex, sex-by-age and age<sup>2</sup> interactions, ancestry (the first four MDS components), diagnostic status (when the cohort followed a case-control design), and dummy variables for scanner (when multiple scanners were used at the same site).

The primary GWAS of regional measures included the global measure of SA or TH as an additional covariate, to test for genetic influences specific to each region. However, to aid interpretation, the regional GWAS were also run without controlling for global measures. Cohort level GWAS results underwent quality control (excluding variants with an imputation  $R^2 \leq 0.5$  and  $MAF \leq 0.005$ ). Across all cohorts, for each phenotype, GWAS summary plots (Manhattan and QQ plots) were visually inspected by the central analysis group; if a given trait showed deviation from expectations that could not be resolved through re-analysis, then that cohort was excluded from analyses of that trait.

### Meta-analysis

The initial meta-analysis was conducted on all of the ENIGMA European cohorts with genome-wide imputed data, and was then meta-analyzed with the UK Biobank European participants to give the principal results. For replication, we took forward the significant variants from the principal results and meta-analyzed them with an additional ENIGMA cohort and results from the CHARGE consortium. We also extracted these variants from a meta-analysis of non-European cohorts to examine generalization of effects across ancestry. Cohort information is provided in table S2. All meta-analyses were conducted using METAL (63). The results of the meta-analyses are summarized in table S5. For the initial and principal meta-analyses we used standard error weighted meta-analyses. In the replication steps we used sample size weighted meta-analyses, in order to include results from the CHARGE consortium for which only sample size weighted results were available. An additional ENIGMA cohort was also included in the sample size weighted meta-analysis because the GWAS was conducted using a program that provided results on an inverse normalized scale. For each meta-analysis, the results were quality controlled, removing strand ambiguous SNPs and INDELS where the effect allele frequency crossed 0.5, and (for the initial meta-analysis) variants where the total sample size was  $< 10,000$ . Independent loci were identified by clumping significant loci in PLINK (72), with thresholds of 1 Mb and  $r^2 < 0.2$ . For the chromosome 17 inversion region this was increased to 10 Mb. For clumping, a random sample of 5,000 unrelated individuals (*plink 1.90* genetic relatedness  $\leq 0.025$ ) of European ancestry from the UK Biobank were used as an LD reference.

Following Rietveld et al. (73), we estimated the variance explained  $R^2$  by each variant  $j$  as:

$$R_j^2 \approx \frac{2p_jq_j \cdot \hat{\beta}_j^2}{\hat{\sigma}_y^2}$$

where  $p_j$  and  $q_j$  are the minor and major allele frequencies,  $\hat{\beta}_j$  is the estimated effect of the variant within the meta-analysis and  $\hat{\sigma}_y^2$  is the estimated variance of the trait (for which we used the pooled variance of the trait across all ENIGMA cohorts and UK Biobank; see table S1). To obtain beta and standard error estimates from the results from the sample size weighted meta-analyses reported in table S5 we used the following equations from Rietveld et al. (73):

$$\hat{\beta}_j \approx z_j \cdot \frac{\hat{\sigma}_y}{\sqrt{N_j \cdot 2p_jq_j}} \text{ and } SE(\hat{\beta}_j) \equiv \frac{z_j}{\hat{\beta}_j}$$

Where  $z_j$  is the Z-score and  $SE(\hat{\beta}_j)$  is the estimated standard effect of the variant within the meta-analysis and  $N$  is the number of contributing alleles.

### *Multiple testing correction*

We analyzed 70 traits (total SA, average TH, and the SA and TH of 34 cortical regions averaged across right and left hemispheres). However, after accounting for the correlation between the traits in the UK Biobank (residuals correcting for sex, age, ancestry and global measures) using matrix spectral decomposition (12), the effective number of traits was estimated to be 60. Therefore, we applied the significance threshold of  $P \leq 8.3 \times 10^{-10}$  to correct for multiple testing in the GWAS meta-analysis results. Multiple testing corrections applied to each of the follow-up analyses are described below.

### Analyses of UK Biobank data

Analyses of the UK Biobank cohort were conducted on the 2018 (version 3) imputed genotypes, imputed to the Haplotype Reference Consortium and merged UK10K and 1000 Genomes (phase 3) panels. UK Biobank bulk imaging data were made available for 12,962 individuals under application #11559 in July 2017, with data from an additional 5,095 individuals made available in August 2019. We processed the raw MRI data using the ENIGMA protocols described above. Following processing, all images were visually inspected. Analyses of UK Biobank participants within 0.02 on the first and second MDS components of the European centroid were included in the meta-analyses of the European ancestry cohorts. Analyses of participants beyond this threshold were included in the meta-analysis of non-European ancestry cohorts.

### Gene-based association analyses

We conducted genome-wide gene-based association analysis using the principal meta-analytic results. We used the 19,427 protein-coding genes from the NCBI 37.3 gene definitions as the basis for the gene-based association analysis using MAGMA (67). For each gene we selected all SNPs within exonic, intronic and untranslated regions as well as SNPs within 50 kb upstream and downstream of the gene. After SNP annotation, there were 18,048 genes that were covered by at least one SNP. Gene-based association tests were performed taking LD between SNPs into account. We applied a Bonferroni correction to account for multiple testing, adjusting for the number of genes tested as well as the effective number of traits tested (60 independent traits), setting the genome-wide threshold for significance at  $4.5 \times 10^{-8}$ . These results are shown in table S6.

### Twin heritability

Twin heritability was estimated in the ENIGMA Queensland Twin Imaging (QTIM) study of healthy adolescent and young adult twins and their siblings (N = 923; 157 MZ pairs, 194 DZ pairs, 221 unpaired twins) using OpenMx (74) in R. Structural equation models were fitted to total SA, average TH, and the SA and TH of 34 cortical regions averaged across right and left hemispheres using full information maximum likelihood to decompose the variance into additive genetic and environmental factors. The models included a simultaneous means regression to adjust for effects of sex, linear and nonlinear age effects, interactions between age and sex, MRI acquisition orientation, and for the regional measures we analyzed a version with and one without the corresponding global measures. We performed analyses without controlling for global measures for completeness. The likelihood ratio test was used to select the best fitting most parsimonious model, which was a model explaining the phenotypic differences in variance by additive genetic factors and unique environmental factors (including measurement error). These results are shown in table S7.

### Heritability due to common variants

For each of the 70 traits, we used LD score regression (64, 65) to estimate the proportion of variance accounted for by common SNPs or SNP heritability ( $h^2_{\text{SNP}}$ ). These results are shown in table S7.

### Partitioned heritability

Partitioned heritability analysis was used to estimate the percentage of heritability explained by annotated regions of the genome (66). Annotations were derived from either Epigenomics Roadmap (22) or a study of chromatin accessibility in mid-fetal brains (21). For analyses using Epigenomics Roadmap data, ChromHMM chromatin states (15 state model) were downloaded for available tissue types ([http://egg2.wustl.edu/roadmap/web\\_portal/chr\\_state\\_learning.html](http://egg2.wustl.edu/roadmap/web_portal/chr_state_learning.html)). For each tissue, genomic regions comprising all active regulatory elements (TssA, TssAflnk, Enh, EnhG) within each tissue type were added as an additional annotation to the baseline model provided with the LDSC package (<https://github.com/bulik/ldsc>). A separate analysis was conducted by identifying if the same active regulatory elements that were specific to either fetal brain (combining annotations from BRN.FET.F and BRN.FET.M) or adult brain cortex (combining annotations from BRN.CING.GYR, BRN.INF.TMP, BRN.ANG.GYR, BRN.DL.PRFRTNL.CRTX). Those elements present in fetal brain showing no overlap with adult brain cortex were used as “fetal brain specific”. Conversely, those elements present in adult brain cortex showing no overlap with fetal brain were used as “adult brain specific”. These annotations were added separately to the baseline model. For analyses using chromatin accessibility in mid-fetal brains, the genomic coordinates of peaks more accessible in the germinal zone than the cortical plate (GZ > CP) and peaks more accessible in the cortical plate than the germinal zone (CP > GZ) were added jointly to the baseline annotations. A separate analysis was conducted subsetting to chromatin accessibility peaks defined in fetal brain that showed evidence of regulating cell-type specifically expressed genes in mid-fetal development. Cell-type definitions and genes with cell-type specific expression (log2 fold change > 0.2 between cell-types, BH corrected  $P < 0.05$ , Expressed in 10% of cells in cluster) were acquired from previously published work (23). Peaks near the TSS of cell-type specific genes (promoter peaks) and those with significant chromatin accessibility correlation with promoter peaks were used as cell-type specific annotations. These annotations of all 16 cell-types were added to the baseline model. Partitioned heritability and the enrichment of heritability explained in these annotations was run using LD score regression (66). The significance of enrichment was corrected across all annotations displayed in each of the analyses using FDR correction ( $\text{FDR} \leq 0.05$ ) and the significance and enrichment scores were plotted (Fig. 2B–D, fig S6A–D).

### Genetic and phenotypic correlations and clustering of genetic correlations

LD score regression (64) was also used to estimate genetic correlations between cortical regions and with global measures. These results are shown in table S14–15. Phenotypic correlations were calculated from the UK Biobank cohort (residuals correcting for sex, age, ancestry, and global brain measures). We used a threshold of  $P \leq 8.3 \times 10^{-4}$  ( $0.05/60$ ) to correct for multiple testing in the genetic and phenotypic correlations shown in Fig. 3.

To identify patterns of genetic correlations of SA and TH (both with and without correction for global measures), we used Mclust (75) for hierarchical cluster analysis, which uses expectation-

maximization to fit parameterized Gaussian mixture models to the data. The best-fitting model for number and shape of clusters was selected as the one with the largest Bayesian Information Criterion. These results are shown in fig. S9.

Genetic correlations were calculated to determine if shared genetic influences contributed to both cortical structure and neuropsychiatric disorders or psychological traits. Summary statistics were downloaded from the following published genome-wide association studies: general cognitive function (54), insomnia (55), antisocial behavior (76), educational attainment (28), subjective well-being (57), depressive symptoms (57), neuroticism (29), attention deficit hyperactivity disorder (ADHD; 56), autism (77), bipolar disorder (78), anorexia nervosa (79), major depressive disorder (58), obsessive compulsive disorder (80), post-traumatic stress disorder (PTSD; 81), schizophrenia (82), anxiety disorders (83), aggression (84), Alzheimer's disease (85), loneliness (86), cigarettes smoked per day (87), epilepsy (88), Parkinson's disease (27), and frontotemporal dementia (69). LD score regression was used to calculate genetic correlations (64). Significance was corrected for multiple comparisons using FDR across all genetic correlations with average TH and total SA, and significant associations were highlighted in Fig. 5A. To explore regional variability in those significant genetic correlations, genetic correlations were conducted between the trait and the cortical regions (without correcting for global measures) are depicted in Fig. 5B.

#### Polygenic risk score analyses

To examine the extent to which our analyses could predict SA and TH in an independent dataset, we derived polygenic risk scores (PRS) from the primary meta-analysis results. Using data from an additional 5,095 unrelated individuals of European ancestry from the UK Biobank who were unrelated to participants who contributed to the meta-analysis (*plink 1.90* genetic relatedness  $\leq 0.025$ ). The index variants used to weight the PRS were identified by clumping the meta-analytic results in *plink 1.90* using an  $r^2$  threshold of 0.1 with a 1000 kb window using the genotypic data of the prediction cohort as a reference. Following checks for strand alignment, PRS were calculated using the probabilistic imputed genotype dosages to account for imputation uncertainty. PRS were calculated for  $P$ -value thresholds of  $P \leq 5 \times 10^{-8}$ ,  $1 \times 10^{-5}$ , 0.001, 0.01, 0.05, 0.1, 0.5, 1. The proportion of variance accounted for by a given PRS was estimated by comparing the  $R^2$  of a linear regression analysis that included the PRS and the covariates that were included in the GWAS analyses to a corresponding analysis that only included the covariates (conducted in *R lm*). The results of these analyses are presented in table S7.

#### Mendelian randomization and latent causal variant analyses

We performed 2-sample Mendelian randomization (2SMR) and latent causal variant (LCV) analyses to investigate whether significant correlations detected by the analyses above could be driven by causal genetic relationships between an exposure (e.g., total surface area) and an outcome (e.g. the correlated traits). The 2SMR analyses were performed using MR-Base (59), which performs a series of MR and sensitivity analyses to evaluate evidence for causality and detect the presence of horizontal pleiotropy (where a SNP directly influences an outcome, violating the MR assumption that SNPs only influence the outcome through their effect on the exposure), and MR-PRESSO (89), which detects and then corrects for horizontal pleiotropy by removing SNPs with outlying effects on the outcome trait. For each exposure trait, we included only SNPs GWAS  $P$ -values  $< 5.0 \times 10^{-8}$  which were clumped for LD ( $r^2 < 0.01$ ) to ensure only significantly exposure-associated, independent variants were included as the instrumental



variables. SNP effects were standardized prior to analysis. We conservatively set the threshold for significance at  $P = 3.13 \times 10^{-3}$  (0.05/16 trait comparisons). Where there was significant evidence of SNP heterogeneity in effect sizes for outcome traits the analyses were re-run in MR-Base with the outlier SNPs removed as further sensitivity analyses to determine the extent to which the relationship between traits was influenced by the outlier SNPs. The results of the MR analyses are presented in table S18. We present the betas and their standard errors for the two associated quantitative traits in the main text following sensitivity analyses suggesting all included instruments (SNPs) were unbiased (59). Additionally, we show odds ratios and 95% confidence intervals reflecting risk per standard deviation increase in the relevant exposure calculated from the inverse variance weighted MR model result in table S18.

A key assumption of MR is that the genetic variants included in the analysis are specific instruments for the exposure under investigation: false positive results can occur in the presence of genetic correlation if the correlation is driven by pleiotropy (19, 90). Additionally, the exposure trait (and also the outcome trait where a causal relationship exists) is likely to be affected by residual genetic variation that doesn't surpass the genome-wide significance threshold. To overcome these potential limitations we also performed latent causal variable analyses using LCV-Master (19). The LCV method mediates genetic correlation through the use of a latent variable that has a causal effect on each trait. The degree of causality of a trait (trait 1) on another (trait 2) is quantified using a *genetic causality proportion* (gcp) that ranges from -1 to 1, with  $\text{gcp} > \text{abs}(0.6)$  implying full or nearly full genetic causality (19). All LCV analyses were performed using genome-wide GWAS summary results (Z-scores) using the default settings. As LCV-Master includes tests for causality in both directions the threshold for significance for these analyses was set at  $P = 6.25 \times 10^{-3}$  (0.05/8 trait comparisons). The LCV results are presented in table S19.

#### Multivariate GWAS analysis

We used TATES (42) to conduct two multivariate analyses: one for the 34 regional SA measures, and a separate analysis for the 34 regional TH measures. These analyses were run on the meta-analytic results from the second phase of meta-analysis. Briefly, TATES combines the *P*-values from univariate GWAS while correcting for the phenotypic correlations between traits and does not require access to raw genotypic data (42). The power of TATES has been shown to be similar or greater than that of multivariate tests using raw data across a range of scenarios for analyses of 20 or more traits (91). For these analyses, we used phenotypic correlations calculated from the UK Biobank cohort (residuals correcting for sex, age, ancestry, and global cortical measures).

#### Gene-set enrichment analyses

Gene-set enrichment analyses were performed on total SA and average TH as well as the multivariate GWAS results for SA and TH using DEPICT (25). Within DEPICT, groups of SNPs were assessed for enrichment in 14,462 gene-sets. These analyses were run using variants with  $P \leq 1.0 \times 10^{-5}$ . Gene-set enrichment analyses were considered significant if they survived FDR correction ( $q \leq 0.05$ ) (25). These results are shown in table S10.

#### Functional annotation

Potential functional impact was investigated for lead variants and their proxies (defined here as  $r^2 > 0.6$  to the lead SNP) at each of the 306 loci nominally associated with global and regional SA and TH using a number of publicly available data sources. The majority of the SNP annotations were as provided by FUMA (30) which annotates:

- SNP location (e.g., genic/intergenic)
- the potential for functional effects through predicted effects as determined by CADD (92) and Regulome (93)
- expression quantitative trait (eQTL) effects. We considered eQTLs within cortical structures from GTEx v7 (94), the UK Brain Expression Consortium (95), the CommonMind Consortium (96), and PsychENCODE (97).
- the presence of enhancers and promoters in SNP regions (RoadMap tissues E053, E073, E081, E082, E125)
- chromatin state and interactions in numerous brain tissues (GEO GSE87112). We included data for dorsolateral prefrontal cortex and neural progenitor cells, PsychENCODE, and adult and fetal cortex (98).

These data were used by FUMA to map coding and non-coding (e.g. lncRNA) genes to each lead SNP and high LD proxies based on an eQTL effect with FDR-corrected  $P$ -values  $\leq 0.05$  in cortical tissue and/or chromatin interactions between the region harboring the lead SNP and a gene promoter in a second chromosomal region (including interactions with an FDR correction  $\leq 1 \times 10^{-6}$ ) (30). Default FUMA settings were used. In the main text we indicate the FDR values for significant eQTL effects (i.e. FDR  $Q \leq 0.05$ : both the nominal  $P$ -values and the FDR-corrected values are provided in table S12). FDR values for adult eQTL data from GTEx reported in text as  $FDR_{GTEx}$  were derived from beta distribution-adjusted empirical  $P$ -values of nominal  $P$ -values from  $t$ -tests of Pearson product-moment correlation coefficients that were FDR corrected using the Storey Tibshirani method (30, 94). FDR values for adult eQTL data from the CommonMind Consortium (CMC) reported in text as  $FDR_{CMC}$  were derived from linear regression coefficient  $t$ -tests that were FDR corrected and accessed by FUMA in  $Q$ -value bins (e.g.  $Q < 1.0 \times 10^{-2}$ ). These bin values are reported as whole numbers by FUMA (e.g. the  $Q < 1.0 \times 10^{-2}$  bin is reported as  $Q = 9.0 \times 10^{-3}$ ). We report the CMC bin value in the main text, although table S12 (FUMA “gene” output) reports the corresponding FUMA-assigned values. For rs1080066, we also investigated if it was reported as an eQTL in adult blood (99), the FDR value reported in text as  $FDR_{BIOS_{genelevel}}$  was derived from meta-analytic  $Z$ -scores and FDR corrected against permuted data. Fetal eQTL data were taken from O’Brien et al (34). FDR values for fetal eQTLs reported in text as  $FDR_{FETAL}$  were derived from nominal  $P$ -values from  $t$ -tests of Pearson product-moment correlation coefficients reported in the original paper that were FDR corrected for our significant loci using the Benjamini-Hochberg method. HaploReg (100) was used to annotate transcription factor binding across multiple tissues, and whether SNPs modified transcription factor binding motifs. The potential for a detrimental effect on protein function due to lead or proxy SNPs located within gene exons was investigated using SIFT and PolyPhen as reported by SNP Nexus (40).

In Fig. 4A we annotate the genomic context of rs1080066 and high LD proxies associated with additional traits, chromatin state in relevant tissues, and gene expression in pre- and post-natal brains. Chromatin state represents the degree to which 200 bp genomic regions are accessible for transcription. Around each of our associated loci chromatin state was annotated by FUMA (30) utilizing the core 15-state model (table S11). In Fig. 4A, genomic regions in three tissues/cells

most relevant to our study (RoadMap E073 dorsolateral prefrontal cortex [Adult cortex], E081 female fetal brain [Fetal brain], and E125 NH-A Astrocytes Primary Cells [Astrocytes]) are indicated as one of the 15 possible chromatin states as predicted by Roadmap Epigenomics using ChromHMM, based on data for 5 chromatin marks (H3K4me3, H3K4me1, H3K36me3, H3K27me3, H3K9me3) in 127 epigenomes (22). Chromatin states are as follows: TssA:Active Transcription Start Site (TSS); TssAFlnk:Flanking Active TSS; TxFlnk:Transcription at gene 5' and 3'; Tx:Strong transcription; TxWk:Weak transcription; EnhG:Genic enhancers; Enh:Enhancers; ZNF/Rpts:ZNF genes & repeats; Het:Heterochromatin; TssBiv:Bivalent/Poised TSS; BivFlnk:Flanking Bivalent TSS/Enhancer; EnhBiv:Bivalent Enhancer; ReprPC:Repressed; PolyComb; ReprPCWk:Weak Repressed PolyComb; Quies:Quiescent/Low. Pre- and post-natal gene expression data across multiple brain regions was obtained from the BrainSpan Atlas of the Developing Human Brain (<http://www.brainspan.org/>). These data include gene expression information for cortical tissues indicated on a scale from low (dark blue) to high (dark red) expression on a  $\log_2$  RPKM scale (RPKM = Reads Per Kilobase [of transcript per] Million [mapped reads], which normalizes expression levels to account for sequencing depth and gene length). The BRAINSPAN cortical tissues, organised in ontological order, are as follows: DFC:dorsolateral prefrontal cortex; VFC:ventrolateral prefrontal cortex; MFC:anterior (rostral) cingulate (medial prefrontal) cortex; OFC:orbital frontal cortex; M1C:primary motor cortex (area M1, area 4); M1C-S1C:primary motor-sensory cortex (samples); PCx:parietal neocortex; S1C:primary somatosensory cortex (area S1, areas 3,1,2); IPC:posteroventral (inferior) parietal cortex; A1C:primary auditory cortex (core); TCx:temporal neocortex; STC:posterior (caudal) superior temporal cortex (area 22c); ITC:inferolateral temporal cortex (area TEv, area 20); Ocx:occipital neocortex; V1C:primary visual cortex (striate cortex, area V1/17).

For each locus, we evaluated functional annotations for the lead SNP and for additional SNPs considered to be credible causal variants (CCVs) if they were either i) in reasonable LD ( $r^2 \geq 0.6$  in individuals of European ancestry) with the lead SNP and/or ii) had  $P$ -values within 2 orders of magnitude of the lead SNP. As lincRNAs show considerable cell/tissue specificity, in the main text we detail SNP location based on neighboring coding genes, but detail lincRNAs when our lead SNPs show eQTL effects and/or chromatin interactions to these non-coding transcripts. Genes at each associated locus were determined to be potential candidates by considering whether the lead SNP (or a proxy) was an eQTL for a particular gene in adult or fetal cortical tissue (listed above) and/or when chromatin interactions were observed to occur between the region harboring the lead/proxy SNPs and a gene promoter in relevant brain tissues (dorsolateral prefrontal cortex and/or neural progenitor cells).

#### Analysis of the central sulcus

To follow-up the precentral surface area association with rs1080066, 10,557 UK Biobank MRI scans were further analyzed using BrainVISA-4.5 Morphologist pipeline for the extraction and parameterization of the central sulcus. Quality controlled FreeSurfer outputs (orig.mgz, ribbon.mgz and talairach.auto) were directly imported into the pipeline to use the same grey and white matter segmentations. Sulci were automatically labeled according to a predefined anatomical nomenclature of 61 sulcal labels per hemisphere (101, 102). Extracted meshes for the left and right central sulcus were visually quality checked; subjects with mislabeled central sulcus were discarded from further analysis; 6,045 individuals had good quality extractions for both the left and right hemispheres. An additional 52 individuals were removed for genotyping

quality or ancestry reasons. The central sulcus depth profile was measured by extending the method introduced in Cykowski et al. (47) and Hopkins et al. (103). The ridges at the fundus of the sulcus and at the convex hull, along with the two extremities, were automatically extracted. Using these landmarks, two coordinate fields (x and y) were extrapolated over the entire mesh surface (104). Sulcal depth was defined as the distance between paired points at the sulcal fundus and brain envelope that shared the same y coordinate (105). For each individual, the parametrized surface was divided into 100 equally spaced points along the length of the sulcus, and the depth at each point was recorded for comparison. We averaged the corresponding depth measurements across the left and right sulcus and calculated the effect of the rs1080066 G allele on the bilaterally averaged depth at each point. These results are shown in Fig. 4D.

### Fine mapping

In order to identify putatively causal variants at each associated locus for future functional validation experiments, we performed fine-mapping with CAVIAR (68). For each associated locus (defined in table S5), all SNPs with  $r^2 > 0.6$  (using 1000G EUR reference panel) to the index SNP for that locus and  $P < 0.001$  to the brain trait of interest were input into the CAVIAR program (v2.2). CAVIAR was then run for each locus specifying two causal variants per locus and using LD patterns from 1000G EUR reference panel to identify the set of SNPs that have a 95% probability of containing the causal variants. These are output in table S13. For those loci where the index SNP was not found in 1000G data, only the index SNP was identified as putatively causal.

## **Supplementary Text**

### The Desikan-Killiany atlas

The Desikan-Killiany atlas (10) used here to define the 34 regions of interest is one of many possible atlases. This atlas was chosen as it is a common output of FreeSurfer, and it is one of the coarser atlases, yielding larger, more consistent regions, defined by the common folding patterns visible on standard MRI. More recent efforts partitioning the cortex into 180 regions have used high-resolution multimodal assessments (MMPC; 106). Other atlases based on functional partitions have also been used, particularly for analyzing function MRI data (107, 108). The breakdown of the cortical surface into 34 large parcels yields clear boundaries between the regions, and allows for anatomically driven quality assessments (see Imaging in the Supplementary Materials and Methods).

The choice of atlas will not have an effect on the global measures; however, the choice of atlas would influence our regional findings, and possibly limit findings, as we may not be able to detect genetic influences on functionally coherent cortical regions, or refined cortical regions partitioned by multimodal MRI measures, for example myelin content, which may have more pathway-specific genetic influences. Assessing the genetic influences on the cortex at a finer scale is an important future effort. However, for multi-cohort efforts such as that performed here, the reliability and accuracy of the parcellations should be assessed across multiple age ranges and MRI acquisition parameters, such as field strength. Automated, and reliable, quality assurance and label accuracy assessments would be an important aspect of this next step.

Our choice of atlas is also likely to influence our findings of regional genetic correlations. It is possible that the correlations between adjacent structures, seen in our analysis, may reflect suboptimal partitioning of the cortex by the atlas; for example, we see a positive genetic correlation between the inferior parietal and the superior parietal gyri, whereas in the MMPC atlas, a portion of each of these two regions is included under a new label, the intraparietal label. Portions of these genetically correlated regions may be re-assigned based on other advanced imaging data, such as multimodal myelin mapping, which may better define cortical cellular architecture.

### Sulcal development

Positive genetic correlations between the SA of neighboring regions may also be driven by the development of the sulcus, separating the regions. The pre- and post- central regions (also known as the primary motor and sensorimotor cortices, respectively) are consistently labeled across many cortical atlases as the regions directly anterior and posterior to the central sulcus, which appears early in development (109). The SA of all four regions surrounding the calcarine sulcus (the pericalcarine, lingual, cuneus, and lateral occipital region) show positive genetic correlations. The same is also true for the SA of the insula and superior temporal gyri surrounding the lateral sulcus (or Sylvian fissure). These major, early-forming sulci show positive genetic correlations between the regions that directly surround them for SA, but not TH. These observations may imply that part of the genetic influences we observe to be underlying regional SA, may actually be driving the formation of the separating folds, or sulci, during fetal development.

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Data used in preparing this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database ([adni.loni.usc.edu](http://adni.loni.usc.edu)). As such, many investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators may be found

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## **Additional Cohort Information**

### 1000BRAINS

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### ADNI1 and ADNI2GO

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative database ([adni.loni.usc.edu](http://adni.loni.usc.edu)). The ADNI was launched in 2003 as a 5-year public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD) and to assess and optimize biomarkers for clinical trials in AD. The initial sample included older adults who were cognitive normal (CN) as well as meeting criteria for MCI and clinical AD. In 2011, ADNI-2 began to recruit an additional CN group as well as individuals with significant memory concerns (SMC), early MCI and late MCI, and AD. These subjects, and others carried forward from ADNI-1, were scanned with an updated neuroimaging protocol. Participants were recruited from over 60 sites across the

U.S. and Canada. For up-to-date information, please see [www.adni-info.org](http://www.adni-info.org). ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

### ALSPAC

Pregnant women resident in Avon, UK with expected dates of delivery 1st April 1991 to 31st December 1992 were invited to take part in the study. The initial number of pregnancies enrolled is 14,541 (for these at least one questionnaire has been returned or a “Children in Focus” clinic had been attended by 19/07/99). Of these initial pregnancies, there was a total of 14,676 fetuses, resulting in 14,062 live births and 13,988 children who were alive at 1 year of age. When the oldest children were approximately 7 years of age, an attempt was made to bolster the initial sample with eligible cases who had failed to join the study originally. As a result, when considering variables collected from the age of seven onwards (and potentially abstracted from obstetric notes) there are data available for more than the 14,541 pregnancies mentioned above. The number of new pregnancies not in the initial sample (known as Phase I enrolment) that are currently represented on the built files and reflecting enrolment status at the age of 18 is 706 (452 and 254 recruited during Phases II and III respectively), resulting in an additional 713 children being enrolled. The phases of enrolment are described in more detail in the cohort profile paper (see footnote 4 below). The total sample size for analyses using any data collected after the age of seven is therefore 15,247 pregnancies, resulting in 15,458 fetuses. Of this total sample of 15,458 fetuses, 14,775 were live births and 14,701 were alive at 1 year of age. A 10% sample of the ALSPAC cohort, known as the Children in Focus (CiF) group, attended clinics at the University of Bristol at various time intervals between 4 to 61 months of age. The CiF group were chosen at random from the last 6 months of ALSPAC births (1432 families attended at least one clinic). Excluded were those mothers who had moved out of the area or were lost to follow-up, and those partaking in another study of infant development in Avon. The data used in the present study were collected from 391 males and further description of this subset and the variables used in this study are provided in Tables S2–S4. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. This publication is the work of the authors and they will serve as guarantors for the contents of this paper. The study website contains details of all the data that is available through a fully searchable data dictionary (<http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/>). Further information can be found in the following papers: Boyd A, Golding J, Macleod J, Lawlor DA, Fraser A, Henderson J, Molloy L, Ness A, Ring S, Davey Smith G. Cohort Profile: The ‘Children of the 90s’; the index offspring of The Avon Longitudinal Study of Parents and Children (ALSPAC). *International Journal of Epidemiology* 2013; 42: 111-127; Fraser A, Macdonald-Wallis C, Tilling K, Boyd A, Golding J, Davey Smith G, Henderson J, Macleod J, Molloy L, Ness A, Ring S, Nelson SM, Lawlor DA. Cohort Profile: The Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. *International Journal of Epidemiology* 2013; 42:97-110.

### BIG

The Brain Imaging Genetics (BIG) database was established in Nijmegen, the Netherlands in 2007. This resource is now part of Cognomics, a joint initiative by researchers of the Donders Centre for Cognitive Neuroimaging, the Human Genetics and Cognitive Neuroscience departments of the Radboud University Medical Center, and the Max Planck Institute for Psycholinguistics (funded by the Max Planck Society). The present study includes two



subsamples of BIG, from successive waves of genotyping on Affymetrix (BIG-Affy) and PsychChip (BIG-PsychChip) arrays. Analyses for this project were carried out on the Dutch national e-infrastructure with the support of SURF Cooperative.

#### GIG

The GIG (Genomic Imaging Göttingen) sample was established at the Center for Translational Research in Systems Neuroscience and Psychiatry (Head: Prof. Dr. O. Gruber) at Göttingen University.

GSP: Brain Genomics Superstruct Project (GSP): Data were provided [in part] by the Brain GSP of Harvard University and the Massachusetts General Hospital, with support from the Center for BrainScience Neuroinformatics Research Group, the Athinoula A. Martinos Center for Biomedical Imaging and the Center for Human Genetic Research. Twenty individual investigators at Harvard and Massachusetts General Hospital generously contributed data to GSP.

#### HUNT

The HUNT Study is a collaboration between HUNT Research Centre (Faculty of Medicine and Movement Sciences, NTNU – Norwegian University of Science and Technology), Nord-Trøndelag County Council, Central Norway Health Authority, and the Norwegian Institute of Public Health.

#### IMpACT

The International Multi-centre persistent ADHD CollaboraTion (IMpACT), is a consortium of clinical and basic researchers from several European countries (The Netherlands, Germany, Spain, Norway, The United Kingdom, Sweden), from the United States of America, and from Brazil.

#### LBC1936

The work was undertaken as part of the Cross Council and University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology (CCACE; <http://www.ccace.ed.ac.uk>). The image acquisition and analysis was performed at the Brain Research Imaging Centre, University of Edinburgh (<http://www.bric.ed.ac.uk>).

#### MPIP

The MPIP Munich Morphometry Sample comprises images acquired as part of the Munich Antidepressant Response Signature (MARS) Study and the Recurrent Unipolar Depression (RUD) Case-Control study performed at the MPIP, and control subjects acquired at the Ludwig-Maximilians-University, Munich, Department of Psychiatry. **PPMI**: Data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database ([www.ppmi-info.org/data](http://www.ppmi-info.org/data)). For up-to-date information on the study, visit [www.ppmi-info.org](http://www.ppmi-info.org).

#### UK Biobank

This research has been conducted using the UK Biobank Resource under Application Number '11559'.

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### International Frontotemporal Dementia GWAS Consortium

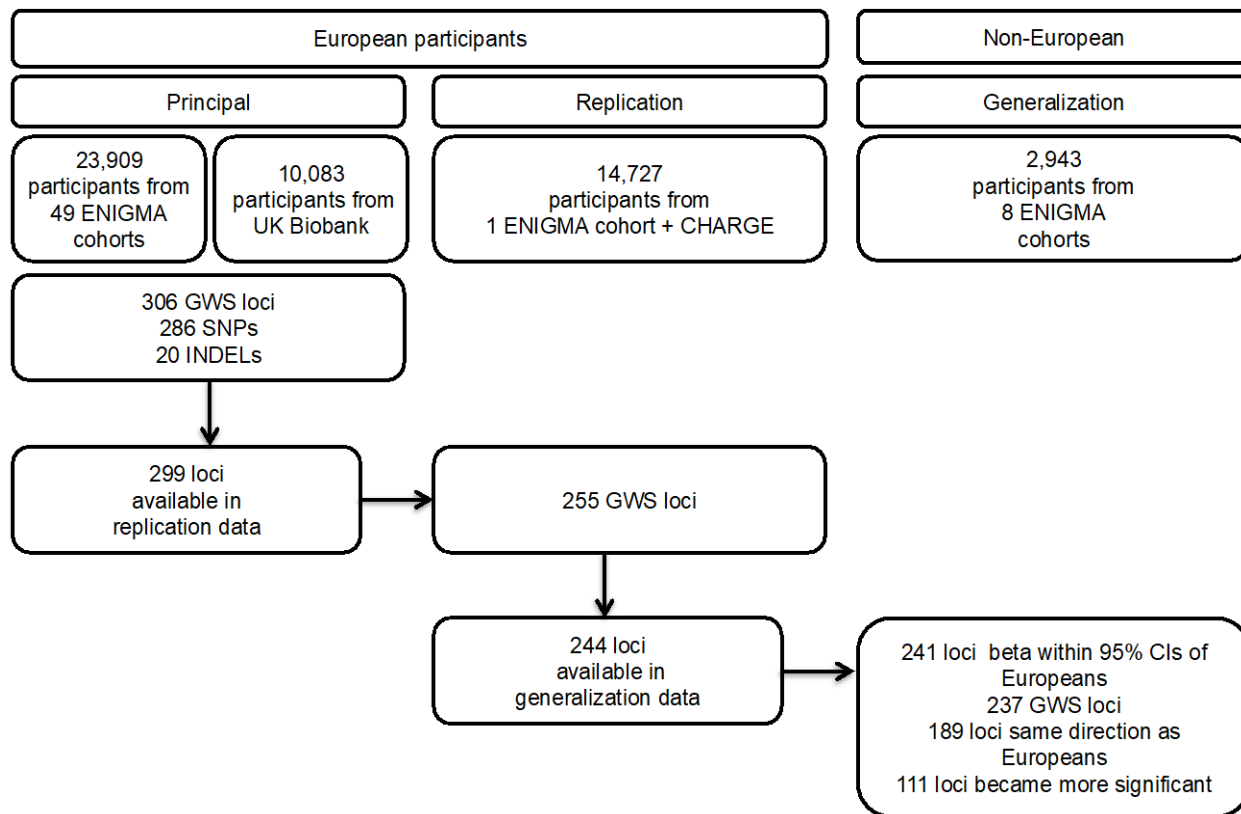
**Authors:** Raffaele Ferrari, Dena G Hernandez, Michael A Nalls, Jonathan D Rohrer, Adaikalavan Ramasamy, John BJ Kwok, Carol Dobson-Stone, William S Brooks, Peter R Schofield, Glenda M Halliday, John R Hodges, Olivier Piguet, Lauren Bartley, Elizabeth Thompson, Eric Haan, Isabel Hernández, Agustín Ruiz, Mercè Boada, Barbara Borroni, Alessandro Padovani, Carlos Cruchaga, Nigel J Cairns, Luisa Benussi, Giuliano Binetti, Roberta Ghidoni, Gianluigi Forloni, Diego Albani, Daniela Galimberti, Chiara Fenoglio, Maria Serpente, Elio Scarpini, Jordi Clarimón, Alberto Lleó, Rafael Blesa, Maria Landqvist Waldö, Karin Nilsson, Christer Nilsson, Ian RA Mackenzie, Ging-Yuek R Hsiung, David MA Mann, Jordan Grafman, Christopher M Morris, Johannes Attems, Ian G McKeith, Alan J Thomas, Pietro Pietrini, Edward D Huey, Eric M Wassermann, Atik Baborie, Evelyn Jaros, Michael C Tierney, Pau Pastor, Cristina Razquin, Sara Ortega-Cubero, Elena Alonso, Robert Perneczky, Janine Diehl-Schmid, Panagiotis Alexopoulos, Alexander Kurz, Innocenzo Rainero, Elisa Rubino, Lorenzo Pinessi, Ekaterina Rogaeva, Peter St George-Hyslop, Giacomina Rossi, Fabrizio Tagliavini, Giorgio Giaccone, James B Rowe, Johannes CM Schlachetzki, James Uphill, John Collinge, Simon Mead, Adrian Danek, Viviana M Van Deerlin, Murray Grossman, John Q Trojanowski, Julie van der Zee, Marc Cruts, Christine Van Broeckhoven, Stefano F Cappa, Isabelle Leber, Didier Hannequin, Véronique Galfier, Martine Vercelletto, Alexis Brice, Benedetta Nacmias, Sandro Sorbi, Silvia Bagnoli, Irene Piaceri, Jørgen E Nielsen, Lena E Hjerfjord, Matthias Riemenschneider, Manuel Mayhaus, Bernd Ibach, Gilles Gasparoni, Sabrina Pichler, Wei Gu, Martin N Rossor, Nick C Fox, Jason D Warren, Maria Grazia Spillantini, Huw R Morris, Patrizia Rizzu, Peter Heutink, Julie S Snowden, Sara Rollinson, Anna Richardson, Alexander Gerhard, Amalia C Bruni, Raffaele Maletta, Francesca Frangipane, Chiara Cupidi, Livia Bernardi, Maria Anfossi, Maura Gallo, Maria Elena Conidi, Nicoletta Smirne, Rosa Rademakers, Matt Baker, Dennis W Dickson, Neill R Graff-Radford, Ronald C Petersen, David Knopman, Keith A Josephs, Bradley F Boeve, Joseph E Parisi, William W Seeley, Bruce L Miller, Anna M Karydas, Howard Rosen, John C van Swieten, Elise GP Dopper, Harro Seelaar, Yolande AL Pijnenburg, Philip Scheltens, Giancarlo Logroschino, Rosa Capozzo, Valeria Novelli, Annibale A Puca, Massimo Franceschi, Alfredo Postiglione, Graziella Milan, Paolo Sorrentino, Mark Kristiansen, Huei-Hsin Chiang, Caroline Graff, Florence Pasquier, Adeline Rollin, Vincent Deramecourt, Thibaud Lebouvier, Dimitrios Kapogiannis, Luigi Ferrucci, Stuart Pickering-Brown, Andrew B Singleton, John Hardy, Parastoo Momeni.

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**Fig. S1.**

Flow chart summarizing the phases of meta-analysis. GWS: genome-wide significant.

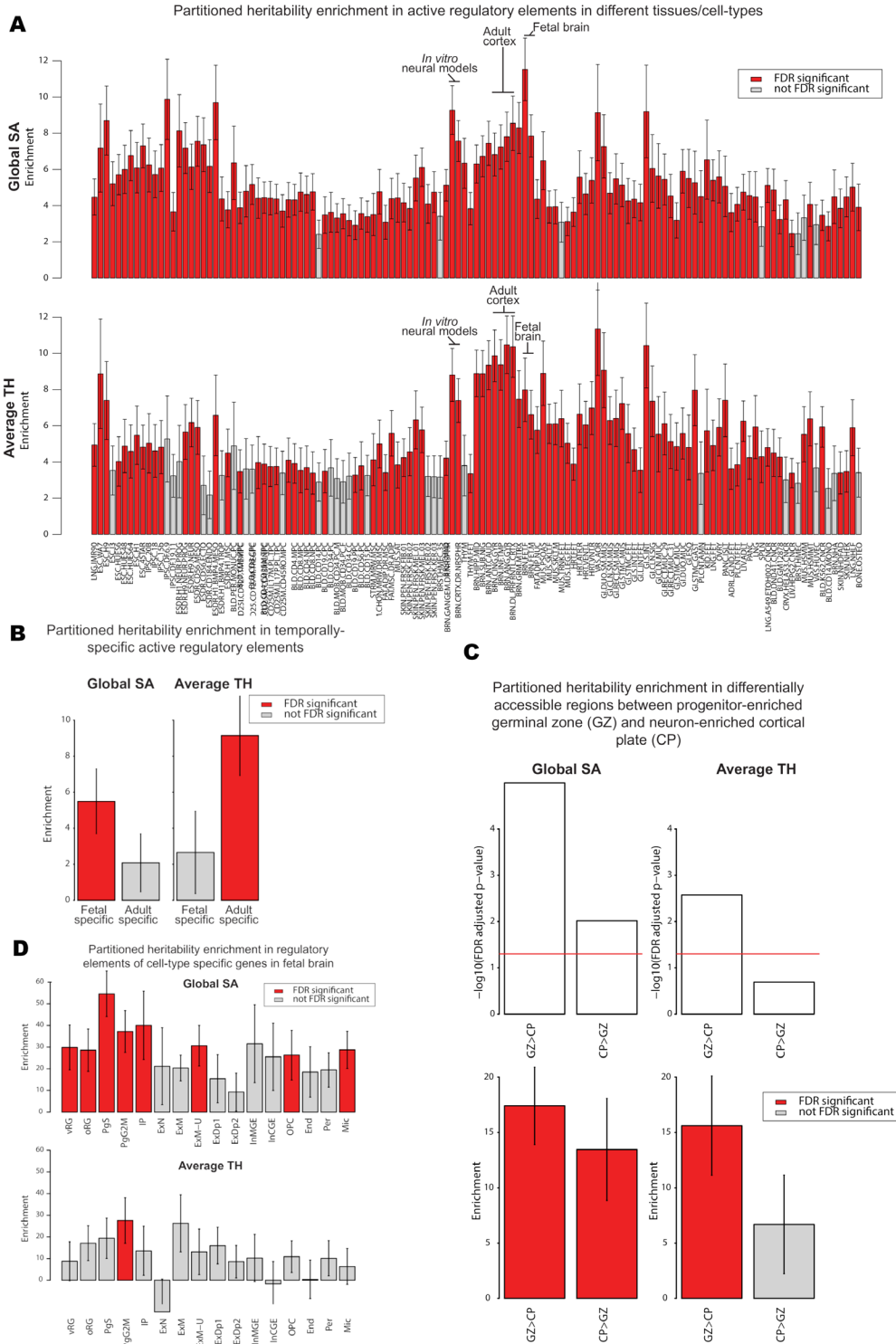
**Fig. S2.** (see external file ManhattanPlots.pdf)  
Manhattan plots of each trait from the principal meta-analysis.

**Fig. S3.** (see external file [QQPlots.pdf](#))  
QQ plots of each region from the principal meta-analysis.



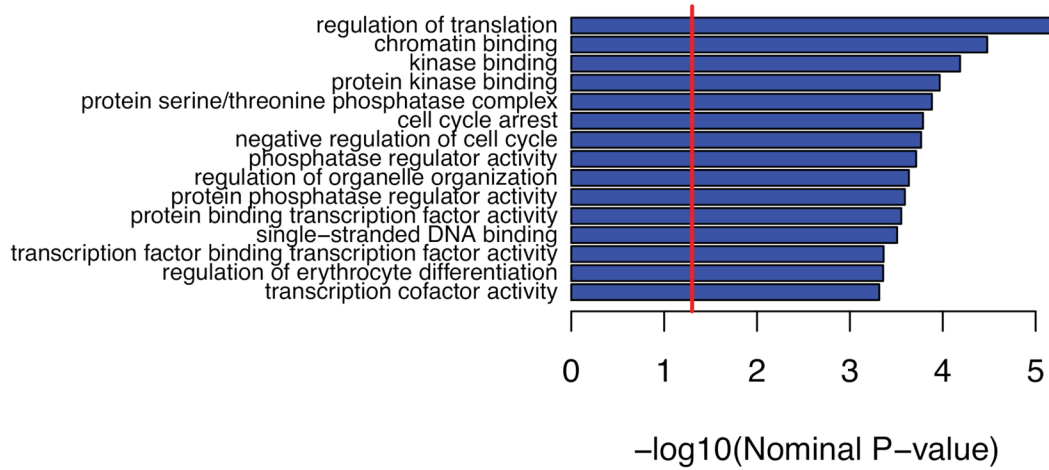
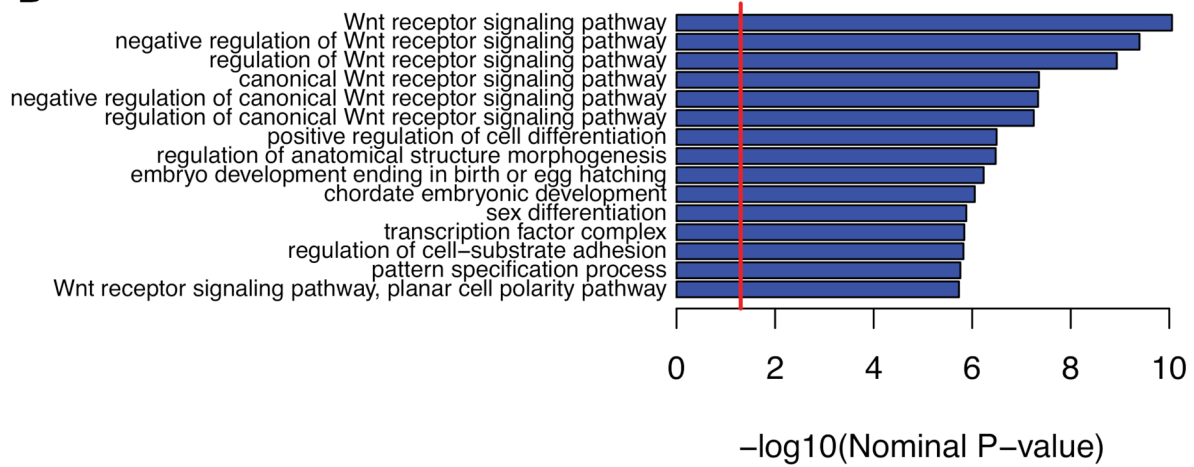
**Fig. S4.** (see external file Forest Plots.pdf).  
Forest plots of the 306 genome-wide significant loci

**Fig. S5.** (see external file LocusZoom.pdf).  
LocusZoom plots of the 306 genome-wide significant loci

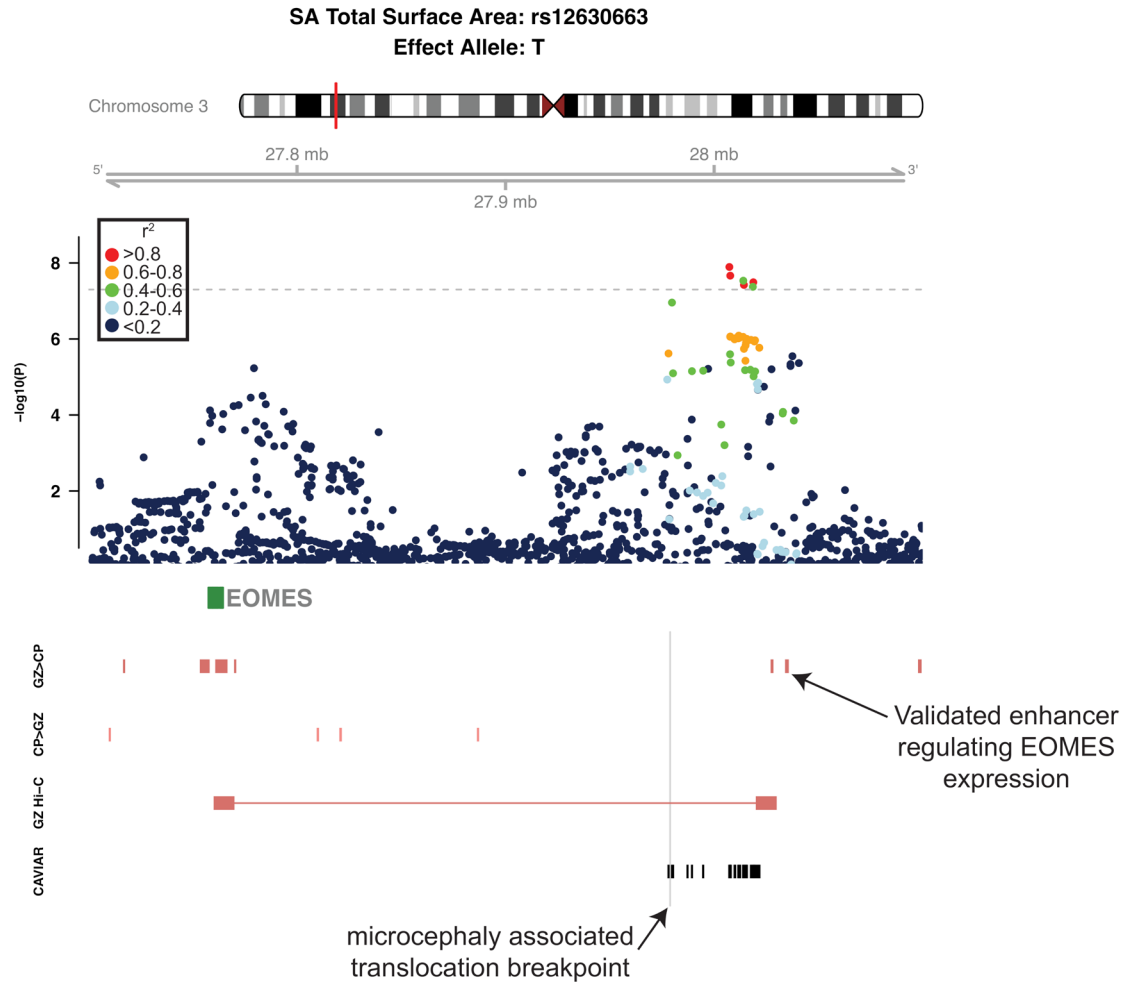


**Fig. S6.**

Partitioned heritability enrichment analyses (A) active regulatory elements across tissues and cell types, (B) temporally specific active regulatory elements, (C) regulatory elements of cell-type specific genes in fetal brain, and (D) differentially accessible regions between progenitor-enriched germinal zone (GZ) and neuron-enriched cortical plate (CP).

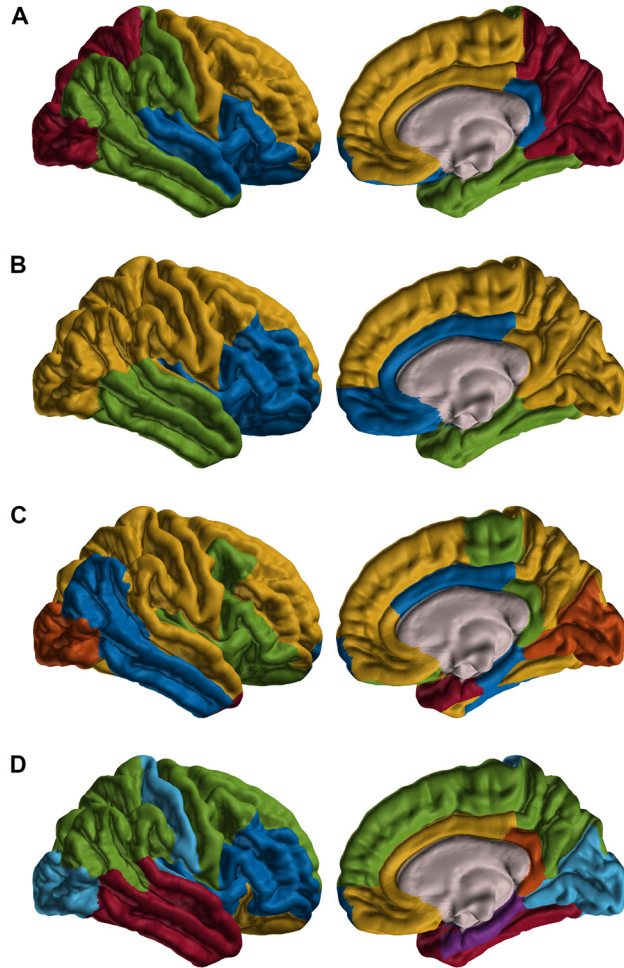
**A****B****Fig. S7.**

Significance of the enrichment of gene ontology annotations for (A) total surface area, and (B) multivariate regional surface area from TATES output.



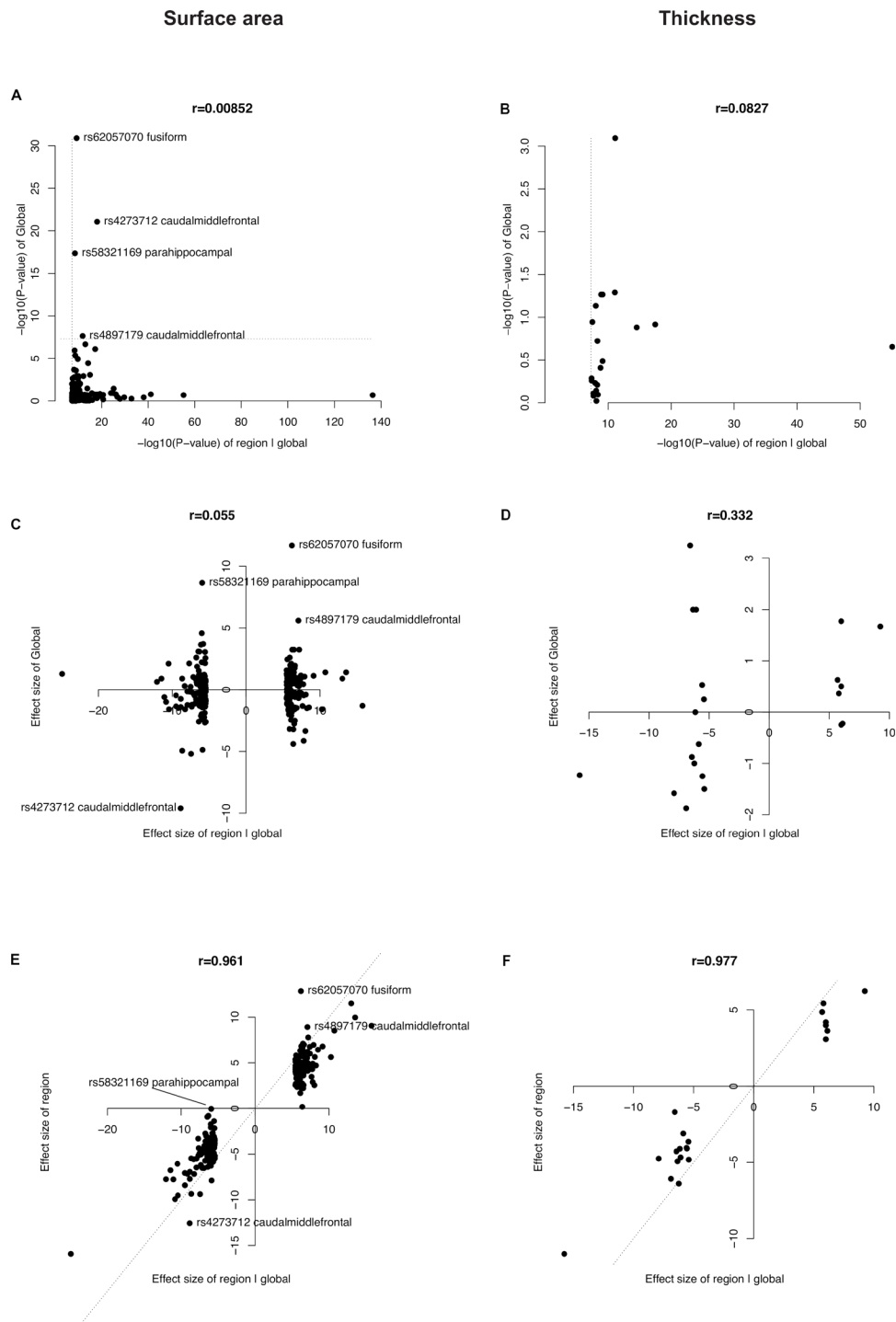
**Fig. S8.**

Regional association plot for the 3p24.1 locus (rs12630663). Localizing EOMES, validated enhancer regulating EOMES expression, chromatin interaction, and microcephaly associated translocation breakpoint.



**Fig. S9.**

Clustering of genetic correlations among (A) surface area and (B) thickness regions after correcting for global measures. Clustering of genetic correlations among (C) surface area and (D) thickness regions without correcting for global measures. The best-fitting model for surface area with global correction was 4 diagonal components with varying volume and shape, and for thickness was 3 spherical components with equal volume. The best-fitting model for surface area without global correction was 5 spherical components with varying volume, and for thickness was 7 diagonal components with equal volume and shape.



**Fig. S10.**

*P*-value of genome-wide significant regional SNPs with global control compared to their *P*-value in the global measure for (A) surface area and (B) thickness. Effect size of genome-wide significant regional SNPs with global control compared to their effect size in global measures for (C) surface area and (D) thickness. Effect size of genome-wide significant regional SNPs with global control compared to regional SNPs without global control in (E) surface area and (F) thickness.

**Fig. S11.** (see external file PhenotypicPlots.pdf)

Phenotypic distribution plots from each cohort and trait included in the meta-analyses.



**Tables S1 to S20** (separate file Grasby\_etal\_Supplementary\_Tables.xlsx).

**Table S1.**

Phenotype descriptions

**Table S2.**

Cohort descriptions

**Table S3.**

Description of the imaging data for each cohort and percentage of individuals retained in each cohort after quality control who were taken forward to the GWAS analyses for each cohort and each trait

**Table S4.**

Description of the genotype data for each cohort

**Table S5.**

Meta-analytic GWAS results for the 306 loci taken forward for replication

**Table S6.**

Results from MAGMA gene based tests

**Table S7.**

Univariate heritability (twin and SNP) for global and regional surface area and thickness

**Table S8.**

Polygenic risk score results for global and regional surface area and thickness

**Table S9.**

Genetic correlations (LD score  $r_G$ ) calculated between global cortical measures and selected morphological traits

**Table S10.**

Results from DEPICT pathway based tests

**Table S11.**

Summary of bioinformatic functional follow-ups

**Table S12.**

eQTL and chromatin interaction information for lead SNPs and proxies

**Table S13.**

Results from CAVIAR fine-mapping

**Table S14.**

Genetic correlations (LD score  $r_G$ ) calculated from the GWAS of regional measures corrected for global measures

**Table S15.**

Genetic correlations (LD score  $r_G$ ) calculated from the GWAS of regional measures not corrected for global measures

**Table S16.**

Genetic correlations (LD score  $r_G$ ) calculated between the imaging phenotypes and selected neuropsychiatric disorders and psychological traits

**Table S17.**

Genetic correlations (LD score  $r_G$ ) calculated between the imaging phenotypes and selected neuropsychiatric disorders and psychological traits on healthy-only participants

**Table S18.**

Mendelian randomization analysis results for total SA and 8 correlated neuropsychological traits

**Table S19.**

Latent causal variable analysis results for total SA against 8 genetically correlated traits

**Table S20.**

Data access statements

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