The genetic architecture of the human cerebral cortex.

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The cerebral cortex underlies our complex cognitive capabilities, yet we know little about the specific genetic loci influencing human cortical structure. To identify genetic variants impacting cortical structure, we conducted a genome-wide association meta-analysis of brain MRI data from 35,660 individuals with replication in 15,578 individuals. We analysed the surface area and average thickness of the whole cortex and 34 regions with known functional specialisations. We identified 206 nominally significant loci ($P \leq 5 \times 10^{-8}$); 150 survived multiple testing correction ($P \leq 8.3 \times 10^{-10}$; 140 surface area; 10 thickness). We found significant enrichment for loci influencing total surface area within regulatory elements active during prenatal cortical development, supporting the radial unit hypothesis. Loci impacting regional surface area cluster near genes in Wnt signalling pathways, known to influence progenitor expansion and areal identity. Variation in cortical structure is genetically correlated with cognitive function, Parkinson's disease, insomnia, depression and ADHD.

The human cerebral cortex is the outer grey matter layer of the brain, which is implicated in multiple aspects of higher cognitive function. Its distinct folding pattern is characterised by convex (*gyral*) and concave (*sulcal*) regions. Computational brain mapping approaches use the consistent folding patterns across individual cortices to label brain regions[1] (Fig. 1a). 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 neurogenic divisions. Variation in global and regional measures of cortical SA and TH are associated with neuropsychiatric disorders and psychological traits[4-6] (Supplementary Table 1). Twin and family-based brain imaging studies show that SA and TH measurements are highly heritable and are largely influenced by independent genetic factors[7,8]. Despite extensive studies of genes impacting cortical structure in model organisms[9], our current understanding of genetic variation impacting human cortical size and patterning is limited to rare, highly penetrant variants[10,11]. These variants often disrupt cortical development, leading to altered post-natal structure. However, little is known about how common genetic variants impact human cortical SA and TH.

To address this, we conducted genome-wide association meta-analyses of cortical SA and TH measures in 51,238 individuals from 58 cohorts from around the world (Supplementary Fig. 1; Supplementary Tables 2–4). Cortical measures were extracted from structural brain MRI scans in regions defined by gyral anatomy using the Desikan-Killiany atlas[12]. Image processing and quality control are described in the Methods. We analysed two global measures, total SA and average TH, and SA and TH for 34 regions averaged across both hemispheres, yielding 70 distinct phenotypes (Fig. 1a; Supplementary Table 1).

Within each cohort genome-wide association (GWAS) for each of the 70 phenotypes was conducted using an additive model (Methods). 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 better localise the global findings, regional GWAS were also run without controlling for global measures. To estimate the multiple testing burden associated with analysing 70 phenotypes, we used matrix spectral decomposition[13], which yielded 60 independent traits (Methods). Therefore, we adopted a significance threshold of $P \leq 8.3 \times 10^{-10}$.

A rolling genome-wide meta-analytic approach was used with three phases (Methods; Supplementary Fig. 1). Initial meta-analysis comprised results from 34 ENIGMA cohorts of European ancestry (19,512 participants) and the UK Biobank[14] (10,083 participants of European ancestry; Methods). The second phase included ten additional ENIGMA cohorts of European ancestry (3,121 participants) submitted after the first meta-analysis. Results of this second phase of meta-analysis were used in all follow-up analyses. The third phase included results from eight

ENIGMA cohorts of non-European ancestry (2,944 participants). We sought further replication from participants of European ancestry for loci reaching $P \leq 5 \times 10^{-8}$ in four additional ENIGMA cohorts (1,628 participants) and with the CHARGE consortium (as a reciprocal replication; 13,950 participants, excluding UK Biobank). High genetic correlations were observed between the meta-analysed ENIGMA European cohorts (excluding UK Biobank) and the UK Biobank cohort using LD-score regression ($rG_{TotalSA} = 1.00$, $P = 2.4 \times 10^{-26}$, $rG_{AverageTH} = 0.94$, $P = 2.5 \times 10^{-19}$) indicating consistent genetic architecture between these 34 ENIGMA cohorts and the single-site, single-scanner UK Biobank cohort.

Across the 70 cortical phenotypes, we identified 213 loci that were nominally genome-wide significant in the second phase of meta-analysis ($P \leq 5 \times 10^{-8}$). Including the non-European cohorts in the meta-analysis yielded an additional 38 loci meeting this threshold, resulting in a total of 251 loci. After including the replication data, 206 loci remained nominally significant (188 influencing SA and 18 influencing TH); 150 of these survived multiple testing ($P \leq 8.3 \times 10^{-10}$; 140 influencing SA and 10 influencing TH; Fig. 1b; Supplementary Table 1; Supplementary Table 5). Significant gene-based association was observed for 479 genes across the 70 cortical phenotypes (Methods; Supplementary Table 6). Figures summarising the meta-analytic results (Manhattan, QQ and Forest plots) are provided in the source data materials.

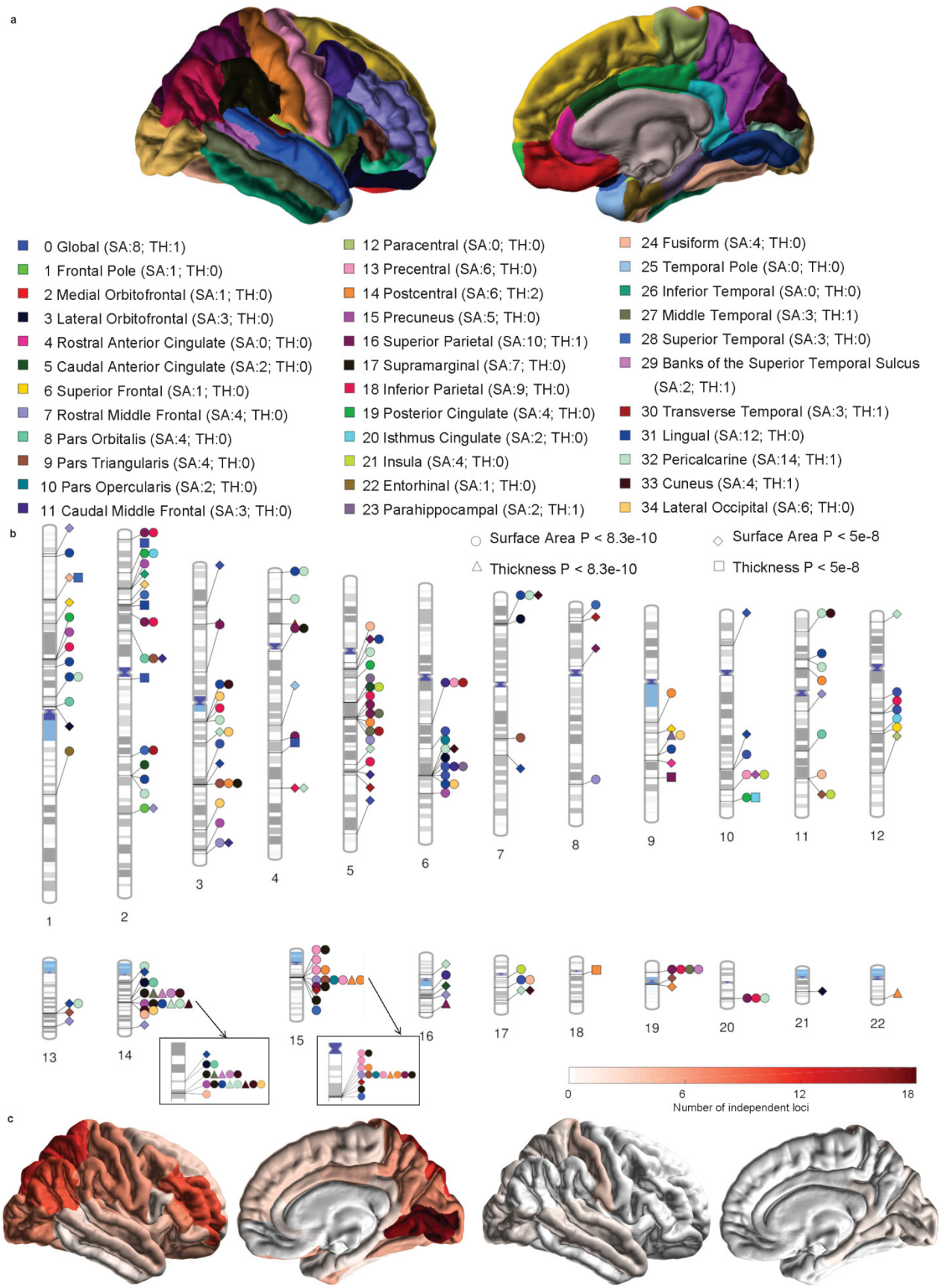

Fig. 1 | Regions of the human cortex and associated genetic loci. a, The 34 cortical regions defined by the Desikan-Killiany atlas[12]; **b**, Ideogram of nominal ($P \leq 5 \times 10^{-8}$) and genome-wide significant loci influencing cortical SA and TH; **c**, Number of genome-wide significant ($P \leq 8.3 \times 10^{-10}$) loci influencing cortical SA and TH.

Genetics of total SA and average TH

Common variants explained 33% (*SE* = 3%) of the variation in total SA and 25% (*SE* = 2%) in average TH, which approaches a third of the heritability estimated from twin and family studies[8] (Methods; Supplementary Table 7). We observed a significant negative genetic correlation between total SA and average TH (r_G = -.32, SE = .05, P = 3.9 x 10^{-11}; Fig. 2a), which persisted after excluding the chromosome 17 inversion region known to influence brain size[15-17] (r_G = -.31, SE = .05, P = 4.7 x 10^{-11}). The direction of this correlation suggests that opposing genetic influences may constrain the total cortical size. The small magnitude of this correlation is consistent with the radial unit hypothesis[10] whereby different developmental mechanisms promote SA and TH expansion.

As expected, total SA showed a positive genetic correlation with intracranial volume (ICV); this correlation remained after controlling for height demonstrating that this relationship is not solely driven by body size (Fig. 2a; Supplementary Table 8). The global cortical measures did not show significant genetic correlations with the volumes of major subcortical structures (Fig. 2a), indicating that variation in cortical and subcortical structures are have predominantly independent genetic influences. This is consistent with known differences in cell-type composition between these structures.

To identify if common variation associated with cortical structure perturbs gene regulation during a specific developmental time period or within a given cell-type, we performed partitioned heritability analyses[18] using sets of gene regulatory annotations from adult and fetal brain tissues[19,20](Methods). The strongest enrichment of the heritability for global SA was seen within areas of active gene regulation (promoters and enhancers) in the mid-fetal human brain (Fig. 2b). We further identified a stronger enrichment in regions of the fetal cortex with more accessible chromatin in the neural progenitor-enriched germinal zone than the neuron-enriched cortical plate[19]. There was also enrichment of active regulatory elements within embryonic stem cells differentiated to neural progenitors[20]. We conducted pathway analyses to determine if there was enrichment of association near genes in known biological pathways (Methods). Among the 241 significant gene-sets there a number were involved in chromatin modification, a process guiding neurodevelopmental fate decisions[21] (Fig. 3c, Supplementary Table 9). These findings suggest that total SA in adults 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]. The strongest evidence of enrichment for average TH was found in active regulatory elements in the adult brain samples, which may reflect processes occurring after mid-fetal development, such as myelination, branching, and pruning[22]. These findings are consistent with the radial unit hypothesis, which proposes that neocortical surface area expansion is largely driven by increases in the neural progenitor pool[3].

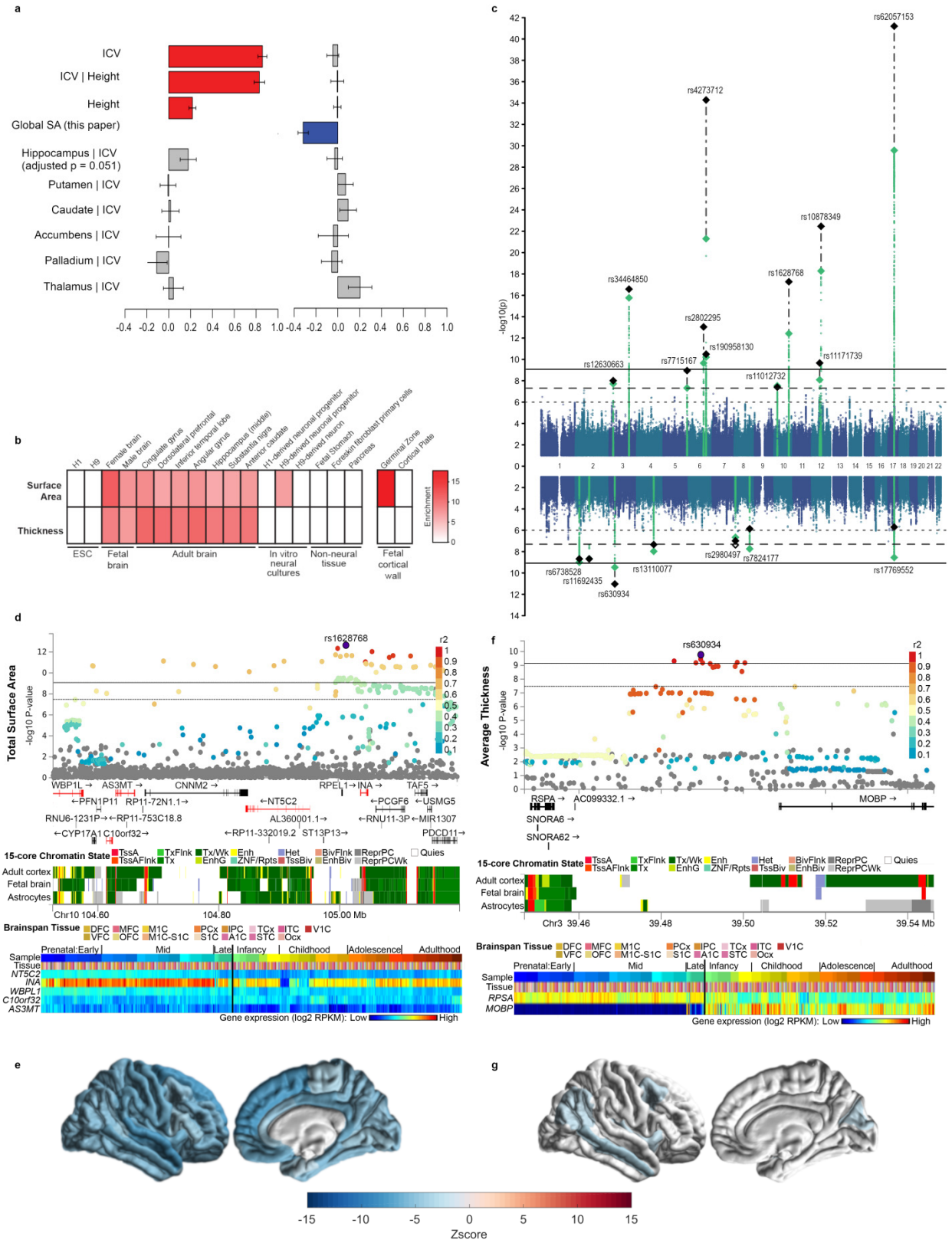

Fig. 2 | Genetics of Global Measures. **a**, Genetic correlations between global measures and selected traits; **b**, Partitioned heritability; **c**, Miami plot of loci associated with global surface area (top) and thickness (bottom), dashes to black diamonds indicate change in P-value after replication; **d**, Regional plot for rs1628768; **e**, rs1628768 (C allele) association with SA of regions without global correction; **f**, Regional plot for rs630934; **g**, rs630934 (A allele) association with TH of regions without global correction. Regional plots include: proxy SNPs and surrounding genes,

chromatin state in RoadMap brain tissues, and BRAINSPAN candidate gene expression in brain tissue.

Loci influencing total SA and average TH

Eleven loci were nominally associated with total SA; eight survived correction for multiple testing (Fig. 2c, Supplementary Table 5). While these loci were significantly associated with global measures the effects were not uniform across regions (Fig. 2e; 2g). Five loci influencing total SA have been previously associated with ICV[16] (Fig. 2c). Of these, rs62057153 (P_{phase2} = 2.7 x 10^{-30}; P_{rep} = 6.3 x 10^{-42}), in the highly pleiotropic chromosome 17q21.31 inversion region[15-17] has previously been associated with Parkinson's disease[23], educational attainment[24], and neuroticism[25] (Supplementary Fig. 2a). On 10q24.33, rs1628768 (P_{phase2} = 3.8 x 10^{-13}; P_{rep} = 5.3 x 10^{-18}) is a cortical expression quantitative trait locus (eQTL)[26] for *WBP1L*, *INA,* and the putative schizophrenia genes *AS3MT* and *NT5C2*[27] (CommonMind Consortium [CMC] FDR P = 0.009; Fig. 2d; Supplementary Table 10–11; Methods). This region has been associated with schizophrenia; however, rs1628768 is in low LD with the schizophrenia-associated SNP, rs11191419 (r^2 = 0.15). The 6q21 locus influencing total SA is intronic to *FOXO3* (which also showed a significant gene-based association with total SA, Supplementary Table 6). The minor allele of the lead variant rs2802295 is associated with decreased total SA (P_{phase2} = 2.3 x 10^{-10}; P_{rep} = 9.2 x 10^{-14}) and has previously been associated with lower general cognitive function[28] (rs2490272: $P_{Cognition}$ = 9.9 x 10^{-14}; $r^2_{rs2802295:rs2490272}$ = 1, Supplementary Fig. 2b). The three loci influencing total SA not previously associated with ICV were rs34464850 (P_{phase2} = 1.7 x 10^{-16}; P_{rep} = 2.6 x 10^{-17}) in proximity to genes *TFDP2* and *ATP1B3*, rs11171739 (P_{phase2} = 8.2 x 10^{-9}; P_{rep} = 2.2 x 10^{-10}) located between *RPS26* and *ERBB3*, and rs190958130 (P_{phase2} = 6.2 x 10^{-11}; P_{rep} = 3.3 x 10^{-11}) near *CENPW* (Supplementary Note).

Among the nominally significant results, the 3p24.1 locus (rs12630663; P_{phase2} = 2.0 x 10^{-8}; P_{rep} = 9.7 x 10^{-9}) is of interest due to its proximity (~200kb) to *EOMES* (also known as *TBR2*), which is expressed specifically in intermediate progenitor cells[29], in the developing fetal cortex[2]. rs12630663 is located in a chromosomal region with chromatin accessibility specific to the human fetal cortex germinal zone of human[19]. This region shows significant chromatin interaction with the *EOMES* promoter[29] and contains numerous regulatory elements that when excised via CRISPR/Cas9 in differentiating neural progenitor cells significantly reduced *EOMES* expression[19]. A rare homozygous chromosomal translocation in the region separating the regulatory elements from *EOMES* silences its expression and causes microcephaly[30] (Supplementary Fig. 5).

Four loci were nominally associated with average TH; only one survived correction for multiple testing (Fig. 2c; Supplementary Table 5). The chromosome 3p22.1 locus (rs630934; P_{phase2} = 3.4 x 10^{-10}; P_{rep} = 9.4 x 10^{-12}) is located between *RPSA* (encoding a 40S ribosomal protein with a potential role as a laminin receptor[31]) and *MOBP* (involved in myelination and differentiation of oligodendrocytes[31]). rs630934 is an eQTL for *MOBP* in tibial nerve (P_{GTEx} = 1.17 x 10^{-13}) and for *RPSA* in multiple tissues including cerebellum ($P_{GTEx_cerebellum}$ = 5.4 x 10^{-6}; Fig. 2f; Supplementary Table 10–11). Among the nominally significant results, the 2q11.2 locus (P_{phase2} = 2.1 x 10^{-9}; P_{rep} = 2.1 x 10^{-9}) is of particular interest because rs11692435 is a missense variant (p.A143V) predicted to impact *ACTR1B* function (Supplementary Table 10–11). *ACTR1B* is expressed in numerous tissue types and is a component of the dynactin complex, necessary for vesicle movement along microtubules[32].

Genetics of regional SA and TH

Within individual cortical regions the amount of phenotypic variance explained by common variants was higher for SA (9–31%) than for TH (0.5–16%) (Fig. 3a–b; Supplementary Table 7). With few exceptions, the genetic correlations between SA and TH within the same region were moderate and negative (Supplementary Table 12–13), suggesting that genetic variants contributing

to the expansion of SA tend to decrease TH. Most genetic correlations between regional surface areas did not survive multiple testing correction, and those that did implied a general pattern of positive correlations between physically adjacent regions and negative correlations with more distal regions (Fig. 3a). This pattern mirrored the phenotypic correlations between regions and was also observed for TH (Fig. 3a–b). The positive genetic correlations were typically between SA of regions surrounding the major, early forming sulci (e.g., pericalcarine, lingual, cuneus, and lateral occipital regions surrounding the calcarine sulcus), which may potentially reflect genetic effects acting on the development of the sulci (see Supplementary Note for further discussion). However, the general pattern of correlations may, in part, depend on the regional partitioning by the Desikan-Killiany atlas[12] (see Supplementary Note for further discussion). Hierarchical clustering of the genetic correlations resulted in a general grouping by physical proximity, with a well-defined cluster in the occipital lobe (Methods; Supplementary Fig. 3).

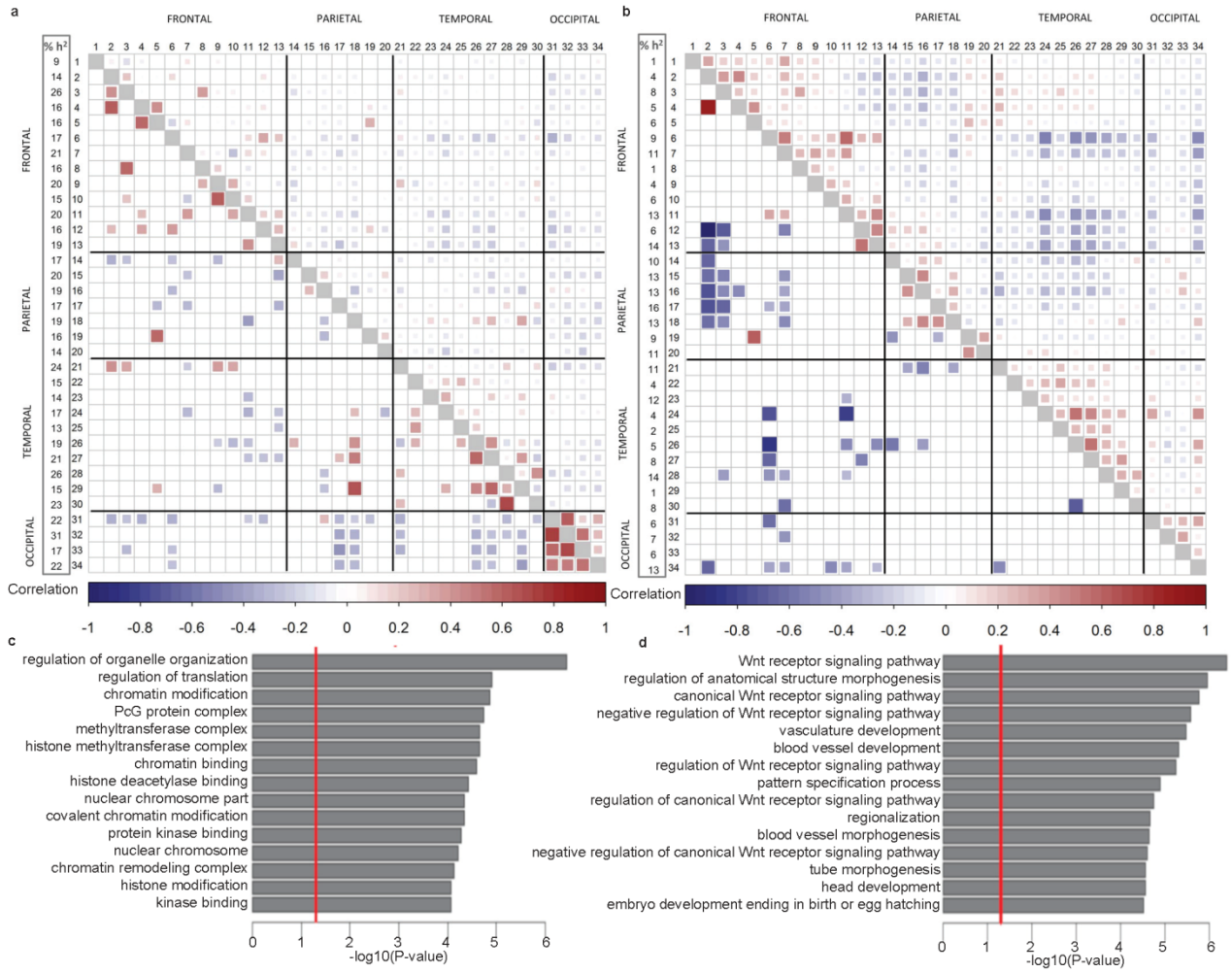

Fig. 3 | Genetic and Phenotypic Correlations Between Cortical Regions. a, Surface Area; **b**, Thickness. The regions are numbered according to the legend of Fig. 1a. The proportion of variance accounted for by common genetic variants is shown in the first column (h2SNP). Phenotypic correlations from the UK Biobank are in the upper triangle. Genetic correlations from the second phase of meta-analysis are in the lower triangle. Only significant correlations are shown. **c**, Enrichment of gene ontology annotations for total surface area; **d**, Enrichment of gene ontology annotations for regional surface area.

To further investigate biological pathways influencing areal identity, we summarised the individual regional results using multivariate GWAS analyses[33] separately for SA and TH that modelled the phenotypic correlations between regions (Methods). Pathway analyses of the multivariate SA

results showed significant enrichment for 493 gene sets (Fig. 3c–d; Supplementary Table 9), many of which are involved in Wnt signalling, with the canonical Wnt signalling pathway showing the strongest enrichment ($P = 3.9 \times 10^{-7}$). Wnt proteins regulate neural progenitor fate decisions[34,35] and are expressed in spatially specific manners influencing areal identity[9]. Pathway analyses of the multivariate TH results did not yield any findings that survived multiple testing.

Loci influencing regional SA and TH

A total of 177 loci were nominally associated with regional SA and 14 with TH; of these 132 SA and 9 TH loci survived multiple testing correction (Supplementary Table 1; Supplementary Table 5). As shown in Fig. 1b, most loci identified were associated with a single cortical region. Of the loci influencing regional measures, few were associated with global measures, and those that were showed effects in the same direction, implying that the significant regional loci were not due to collider bias[36] (Supplementary Fig. 4).

The strongest regional association was observed on chromosome 15q14 with the precentral SA (rs1080066, $P_{phase2} = 6.9 \times 10^{-132}$; $P_{rep} = 4.4 \times 10^{-188}$; variance explained = 0.87% Fig. 4a–b). Across traits within the 15q14 region we observed 14 independent significant associations from six LD blocks (r^2 threshold ≤ .02; see Fig. 4b, Supplementary Table 1; Supplementary Table 5). As we observed strong association with the SA of both pre- and post-central gyri, we localised the association within the central sulcus in 5,993 unrelated individuals from the UK Biobank (Methods). The maximal association between rs1080066 and sulcal depth was observed around the *pli de passage fronto-pariétal moyen* ($P = 7.9 \times 10^{-21}$), a region associated with hand fine-motor function in humans[37] and shows distinct depth patterns across different species of primates[38] (Fig. 4d). Located in a large intergenic region rs1080066 is an eQTL for the downstream gene *THBS1* in whole blood ($P_{\mathrm{BIOS_genelevel}} = 1.5 \times 10^{-9}$) with evidence of chromatin interaction between the rs1080066 region and the *THBS1* promoter in neural progenitor cells (Fig. 4a).

Across the 14q23.1 region, we observed 14 significant associations from three loci (Fig. 4e–f; Supplementary Table 1; Supplementary Table 5). Within this region, our strongest association was observed with the precuneus SA (rs73313052: $P_{phase2} = 1.7 \times 10^{-23}$; $P_{rep} = 2.5 \times 10^{-35}$; variance explained = 0.28%). rs73313052 is located between *DACT1* and *DAAM1*, both of which are involved in synapse formation and are critical members of the Wnt signalling cascade[39,40]. rs73313052 is an eQTL for *DAAM1* in adult cortex (FDR $P_{\mathrm{CMC_SVA}} = 0.009$), with high LD proxies located within an active transcription start site in adult cortex and fetal brain tissue (Fig. 4e; Supplementary Table 10–11). Consistent with enrichment in the pathway analyses, a number of other loci were located in regions with functional links to genes involved in Wnt signalling, including 1p13.2, where rs910697 (lingual SA, $P_{phase2} = 5.0 \times 10^{-11}$; $P_{rep} = 1.1 \times 10^{-11}$; a synonymous SNP in *WNT2B* exon 4) and rs2999158 (pericalcarine SA, $P_{phase2} = 2.0 \times 10^{-12}$; $P_{rep} = 1.1 \times 10^{-15}$) are cortical eQTLs for *ST7L* and *WNT2B* (FDR $P_{\mathrm{CMC_SVA}} = 0.009$; Supplementary Table 10–11).

A number of other regional associations occur near genes with known roles in brain development. For example, on chromosome 1p22.2, rs1413536 (inferior parietal SA: $P_{phase2} = 9.7 \times 10^{-13}$; $P_{rep} = 2.8 \times 10^{-14}$) is a cortical eQTL for *LMO4* (FDR $P_{\mathrm{CMC_SVA}} = 0.049$). There are chromatin interactions between the region housing both this SNP and rs11161942 (posterior cingulate SA: $P_{phase2} = 2.8 \times 10^{-10}$; $P_{rep} = 4.4 \times 10^{-10}$) and the *LMO4* promoter in neural progenitor cells (Supplementary Table 10–11). *Lmo4* is one of the few genes already known to be involved in areal identity specification in mammalian brain[41].

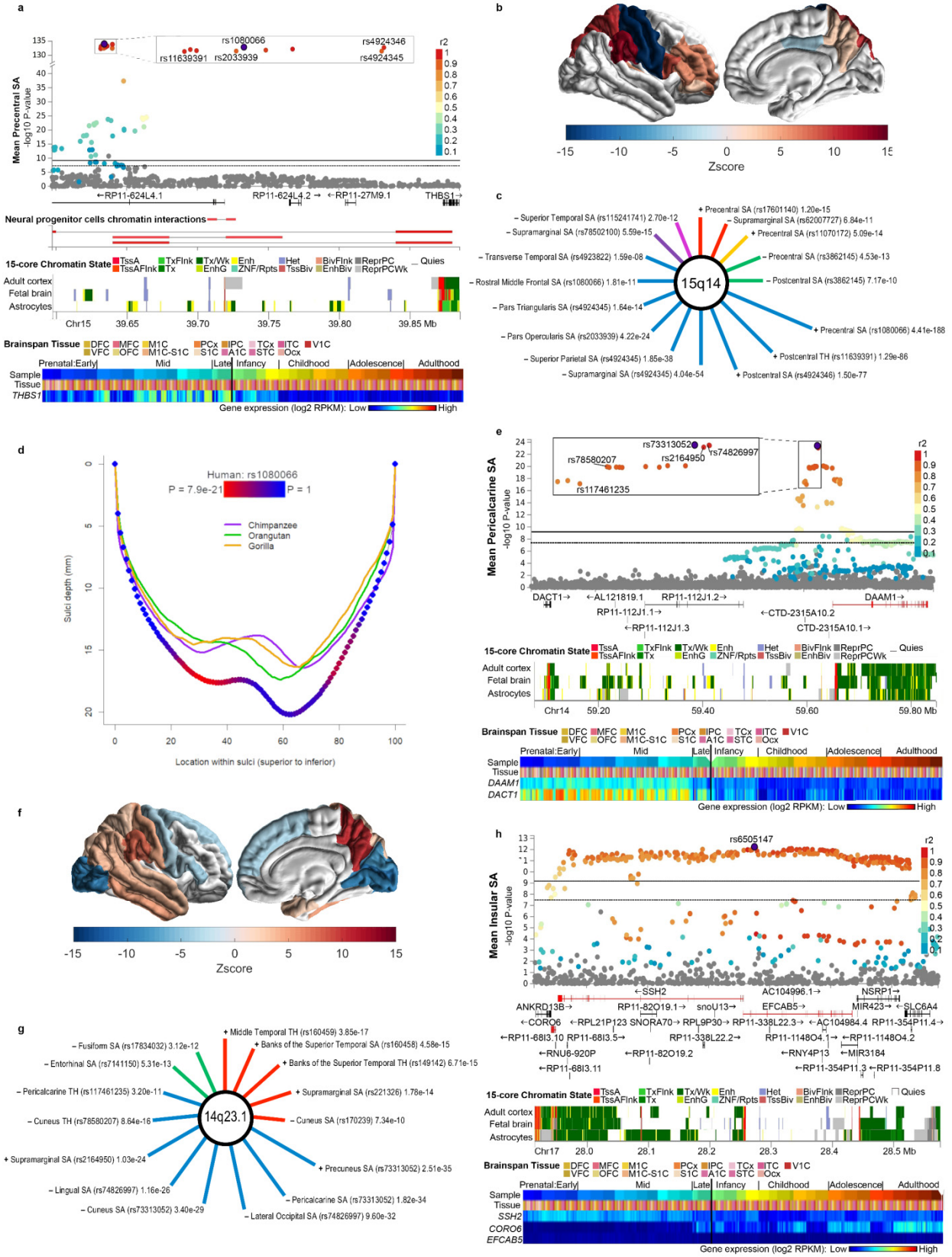

Fig. 4 | Genetics of Regional Measures. a, Regional plot for rs1080066; **b**, rs1080066 (G allele) association with SA of regions; **c**, Sun plot of regions associated with 15q14; **d**, rs1080066 association with central sulcus depth and depth of several primate species; **e**, Regional plot for rs73313052; **f**, Association of rs73313052 (A allele) with SA of regions; **g**, Sun plot of regions associated with 14q23.1; **h**, Regional plot for rs6505147. Regional plots include: proxy SNPs and

surrounding genes, chromatin state in RoadMap brain tissues, and BRAINSPAN candidate gene expression in brain tissue. Sun plot colours indicate different LD-blocks.

Another locus of interest is chromosome 17q11.2 (Fig. 4g) where the lead variant, rs6505147 (P_{phase2} = 4.0 x 10^{-13}; P_{rep} = 1.2 x 10^{-12}), is associated with the insular SA. Located in *EFCAB5*, rs6505147 is centromeric to the serotonin transporter *SLC6A4*. Both *SLC6A4* and the insula have been implicated in mood disorders (although support for SLC6A4 is equivocal)[42-44]. rs6505147 is in a large LD block that extends to *SLC6A4*, but is not in LD (r^2=.06) with the highly investigated 5-HTTLPR repeat polymorphism that is within *SLC6A4* (see Methods). rs6505147 is a cortical eQTLs in multiple databases for six genes flanking *SLC6A4* (*CORO6*, *SSH2*, *EFCAB5*, *BLMH*, *GOSR1*, *SUZ12P*), but not for *SLC6A4* itself (Supplementary Table 10–11). While the LD structure at this locus complicates the assignment of a candidate gene (Methods), increased *EFCAB5* expression was recently associated with delayed brain aging, highlighting a possible role for this gene in the human aging[45].

Genetic correlations with other traits

To examine shared genetic effects between cortical structure and other traits, we performed genetic correlation analyses with GWAS summary statistics from 24 selected traits (Methods). We observed significant positive genetic correlations between total SA and general cognitive function[28], educational attainment[24], and Parkinson's disease[23]. For total SA, significant negative genetic correlations were detected with insomnia[46], attention deficit hyperactivity disorder[47] (ADHD), depressive symptoms[48], major depressive disorder[49], and neuroticism[25]. Genetic correlations with average TH did not survive multiple testing correction due to the weaker genetic association seen in the TH analyses (Fig. 5; Supplementary Table 14). We mapped genetic correlation patterns across the cortical regions without correction for the global measures to map the magnitude of these effects across the brain. No additional neuropsychiatric or psychological traits were significant at a regional level.

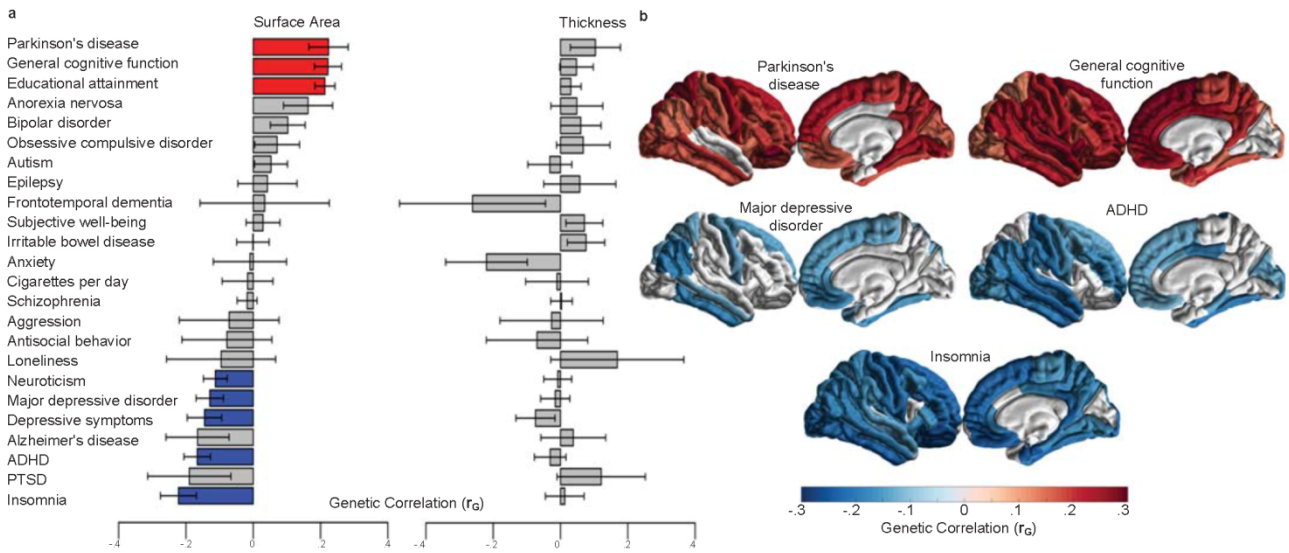

Fig. 5 | Genetic correlations with neuropsychiatric and psychological traits. a, genetic correlations with total SA and average TH positive correlations are shown in red, while negative correlations are shown in blue; **b**, regional variation in the strength of genetic correlations between regional surface area (without correction for total surface area) and traits showing significant genetic correlations with total surface area.

Discussion

Here we present a large-scale collaborative investigation of the effects of common genetic variation on human cortical structure using data from 51,238 individuals from 58 cohorts from around the world. We identify specific loci influencing cortical surface area (with 140 loci surviving multiple testing) and thickness (10 loci), implicating genes involved in areal patterning and cortical development. Our results support the radial unit hypothesis of surface area expansion in humans[3]: genetic variation within regulatory elements in fetal neural progenitor cells[19] is associated with variability in adult cortical surface area. We also find that Wnt signalling genes influence areal expansion in humans, as has been reported in model organisms such as mice[9]. Cortical thickness 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 to map the involvement of specific genes. Genetic variation associated with brain structure is functionally relevant, as evidenced by genetic correlations with a range of neuropsychiatric disorders and psychological traits, including general cognitive function, Parkinson's disease, depression, ADHD and insomnia. This work identifies novel genome-wide significant loci associated with cortical surface area and thickness based on the largest imaging genetics study to date, providing a deeper understanding of the genetic architecture of the human cerebral cortex and its patterning.

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Methods

Ethical approval and data availability

Participants in all cohorts in this study gave written informed consent and sites involved 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*). The meta-analytic results will be available to download from the ENIGMA consortium webpage upon publication http://enigma.ini.usc.edu/research/download-enigma-gwas-results.

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] (see Supplementary Table 3). SA and TH were quantified for each subject within 34 distinct gyral-defined regions in each brain hemisphere according to the Desikan-Killiany atlas[12] (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 reported for all measures with the exception of the frontal and temporal poles[8]. Image processing and quality control were implemented at the cohort level following detailed, harmonized protocols (see http://enigma.ini.usc.edu/protocols/imaging-protocols/ for protocols); phenotype distributions for all traits in all cohorts were inspected centrally prior to meta-analysis any cohort where the phenotypic distribution for a given trait showed deviation from expectations that could not be resolved through reanalysis 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[50] or Haplotype Reference Consortium[51] references (Supplementary Table 4). 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, sex, ancestry (the first four MDS components), diagnostic status (when the cohort followed a case-control design), and 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 $R^2 \leq .5$ and MAF $\leq .005$). 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 reanalysis that cohort was excluded from analyses of that trait. Given the large disparity in sample size (and corresponding fluctuation in power) between indels and SNPs (see UK Biobank data below), we only carried forward SNPs within the meta-analyses.

Multiple testing correction

We analysed 70 traits (total SA, average TH, and the SA and TH of 34 cortical regions averaged across right and left). 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 (matSpD[13]) 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.

Meta-analysis

A rolling meta-analytic approach was used, where three phases of meta-analysis were conducted. The meta-analytic workflow is described in Supplementary Fig. 1 and cohort information is provided in Supplementary Table 2. All meta-analyses were conducted using METAL[52]. The results of the meta-analysis are summarized in Supplementary Table 5. For meta-analyses phases 1–3 we used standard error weighted meta-analyses. In the additional replication step, 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. For each meta-analysis, the results were quality controlled, removing strand ambiguous SNPs where the effect allele frequency crossed .5, and variants where the total sample size was < 10,000 for phases 1–3. Independent loci were identified initially by clumping significant loci in PLINK[53], with thresholds of 100 Mb and $r^2 < .2$. This was refined using cojo, step-wise model selection, in GCTA[54]. For clumping and cojo, the1000 Genomes Project Phase 3 version 5 was used as an LD reference.

We visually inspected the frequencies of effect alleles of all nominally genome-wide significant ($P \leq 5 \times 10^{-8}$) variants that were strand ambiguous. Three variants (rs10237366: lingual and pericalcarine SA, rs2269084: paracentral SA, rs4515470: superior temporal SA) showed allele frequency patterns that could not be disambiguated for one or more of the non-European cohorts. In these cases, the data for the variant within the cohort(s) that could not be resolved were dropped and the meta-analysis was re-run.

Following Rietveld et al[55], we estimated the variance explained R^2 by each variant j as:

$$R_j^2 \approx \frac{2p_j q_j . \hat{\beta}_j^2}{\hat{\sigma}_y^2}$$

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 Supplementary Table 1). To obtain beta and standard error estimates from the results from the sample size weighted meta-analyses reported in Supplementary Table 5 we used the following equations from Rietveld et al[55]:

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

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.

Analyses of UK Biobank data

Analyses of the UK Biobank cohort were conducted on the 2017 imputed genotypes restricted to variants present in the Haplotype Reference Consortium[51]. UK Biobank bulk imaging data were made available for 12,962 individuals under application #11559 in July 2017. We processed the raw MRI data using the ENIGMA protocols. Following processing, all images were visually inspected. Analyses of UK Biobank participants within .02 on the first and second MDS components of the European centroid were included in the phase 1 meta-analyses of the European ancestry cohorts (Supplementary Fig. 1). Analyses of participants beyond this threshold were included in the phase 3 meta-analyses of non-European ancestry cohorts (see Supplementary Fig. 1).

Gene-based association analyses

We conducted genome-wide gene-based association analysis using the second phase of the 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[56]. We selected for each gene all SNPs within exonic, intronic and untranslated regions of the gene as well as SNPs within 50 kb downstream and upstream of the gene. After SNP annotation, there were 18,295 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 number of traits tested (60 independent traits), setting the genome-wide threshold for significance at 4.5×10^{-8}. These results are shown in Supplementary Table 6.

Heritability due to common variants, genetic correlations and partitioned heritability

We used LD score regression[57,58] to estimate the proportion of variance accounted for by common SNPs or SNP heritability (h^2_{SNP}) of the global measures (total SA and average TH) and the SA and TH of each of the 34 cortical regions. These results are shown in Supplementary Table 7. LD score regression[58] was also used to estimate genetic correlations between regions and with global measures. These results are shown in Supplementary Table 12–13. 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[59] for hierarchical cluster analysis, which uses expectation-maximisation 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 Supplementary Fig. 3.

Partitioned heritability analysis was used to estimate the percentage of heritability explained by annotated regions of the genome[60]. Annotations were derived from either Epigenomics Roadmap[20] or a study of chromatin accessibility in mid-fetal brains[19]. For analyses using Epigenomics Roadmap data, chromatin states (15 state model) were downloaded for available tissue types (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). 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 separately to the baseline annotations. Partitioned heritability and the enrichment of heritability explained in these annotations was run using LD score regression[60]. The significance of enrichment was corrected across all annotations used (including those not displayed) using false discovery rate (FDR) and the enrichment scores were plotted as a heatmap for those that survived significance (Fig. 2b).

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[28], insomnia[46], antisocial behavior[61], educational attainment[24], subjective well-being[48], depressive symptoms[48], neuroticism[25], attention deficit hyperactivity disorder (ADHD)[47], autism[62], bipolar disorder[63], anorexia nervosa[64], major depressive disorder[49], obsessive compulsive disorder[65], post-traumatic stress disorder (PTSD)[66], schizophrenia[67], anxiety disorders[68], aggression[69], Alzheimer's disease[70], loneliness[71], cigarettes smoked per day[72], epilepsy[73], Parkinson's disease[23], frontotemporal dementia[74], and irritable bowel disease[75]. LD score regression was used to calculate genetic correlations[58]. 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. 5. 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). These results are shown in Supplementary Tables 8 and 14.

Multivariate GWAS analysis
We used TATES[33] to conduct two multivariate analyses: one for the 34 regional SA measures, and one 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[33]. 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[76]. For these analyses, we used phenotypic correlations calculated from the UK Biobank cohort (residuals correcting for sex, age, ancestry, and global brain 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[77]. 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 ($q \leq 0.05$)[77]. These results are shown in Supplementary Table 9.

Functional annotation
Potential functional impact was investigated for each of the 251 SNPs nominally associated with global and regional SA and TH and for their proxies (defined here as $r^2 > 0.6$ to the lead SNP) using a number of publicly available data sources. The majority of the SNP annotations were as provided by FUMA[26] which annotates SNP location (e.g., genic/intergenic), the potential for functional effects through predicted effects as determined by CADD[78] and Regulome[79], expression quantitative trait (eQTL) effects (e.g., GTEx, the UK Brain Expression Consortium (http://www.braineac.org/), and the CommonMind Consortium[81]), and chromatin state and interactions in numerous tissues (data from 21 tissue/cell types, GEO GSE87112). These data were used by FUMA to map coding and non-coding (e.g., lincRNA) genes to each lead SNP based on an eQTL effect with an FDR correction $P \leq 0.05$ in cortical tissue, and/or chromatin interactions between the region harbouring the lead SNP and a gene promoter in a second chromosomal region (including interactions with an FDR correction $P \leq 1 \times 10^{-6}$) in dorsolateral prefrontal cortex and neural progenitor cells[26]. HaploReg[80] 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 SNPNexus[81]. 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/). Summaries of the functional annotation data are presented in Supplementary Tables 10–11.

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 gray and white matter segmentations. Sulci were automatically labeled according to a predefined anatomical nomenclature of 60 sulcal labels per hemisphere[82,83]. Extracted meshes for the left and right central sulcus were visually quality checked; subjects with mislabelled central sulcus were discarded from further analysis; 6,045 individuals had good quality extractions for both the left and right hemispheres. The central sulcus depth profile was measured by extending the method introduced in[37,84]. 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[85]. Sulcal depth was defined as the distance between paired points at the sulcal fundus

and brain envelope that shared the same y coordinate[86]. 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.

Estimating linkage disequilibrium with the 5-HTTLPR variable number tandem repeat.
Using PLINK[53], we estimated the LD between rs6505147 and the 5-HTTLPR variable number tandem repeat using data from 807 unrelated founders from the QTIM sample who are genotyped for 5-HTTLPR and have rs6505147 imputed (imputation accuracy r^2 = 0.965). These analyses showed the two genotypes to be unlinked, r^2 = 0.066, D' = 0.267.

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Supplementary Figures
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Supplementary Figure 4. 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.
Supplementary Figure 5. Regional association plot for the 3p24.1 locus (rs12630663)

Supplementary Notes
Functional annotation
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[26] utilising the core 15-state model as predicted by Roadmap Epignomics using ChromHMM, based on data for 5 chromatin state marks (H3K4me3, H3K4me1, H3K36me3, H3K27me3, H3K9me3) in 127 epigenomes[20]. In Fig. 5, 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 outlined in Table 1.

Table 1. RoadMap Core 15-chromatin state model abbreviations and descriptors

STATE #	Abbreviation	Description
1	TssA	Active Transcription Start Site (TSS)
2	TssAFlnk	Flanking Active TSS
3	TxFlnk	Transcription at gene 5' and 3'
4	Tx	Strong transcription
5	TxWk	Weak transcription
6	EnhG	Genic enhancers
7	Enh	Enhancers
8	ZNF/Rpts	ZNF genes & repeats
9	Het	Heterochromatin
10	TssBiv	Bivalent/Poised TSS
11	BivFlnk	Flanking Bivalent TSS/Enhancer
12	EnhBiv	Bivalent Enhancer
13	ReprPC	Repressed PolyComb
14	ReprPCWk	Weak Repressed PolyComb
15	Quies	Quiescent/Low

To aid in the identification of candidate genes influencing cortical development we examined gene expression levels in pre- and post-natal brains for each of the genes of interest (primarily cortical eQTLs and/or genes with a known brain association/function) flanking our associated loci. Here we used data included in the Developmental Transcriptome portal of the BRAINSPAN Atlas of the Developing Human Brain website (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 normalises expression levels to account for sequencing depth and gene length). The BRAINSPAN cortical tissues, organised in ontological order, are as outlined in Table 2.

Table 2. Brainspan cortical tissues abbreviations and descriptors

Abbreviation	Description
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 neighbouring 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 cortical tissue (e.g. BRAINEAC, CMC or GTEx cortical tissues) and/or when chromatin interactions were observed to occur between the region harbouring the lead/proxy SNPs and a gene promoter in relevant brain tissues (dorsolateral prefrontal cortex and/or neural progenitor cells). For each of the loci shown in the main text we determined potential candidates as (but not limited to) the following:

Loci associated with Total Surface Area:

rs62057153, chromosome 17q21.31

Located in intron 4 of the Corticotropin Releasing Hormone Receptor 1(*CRHR1*) gene, lead SNP rs62057153 is in a large inversion region with extensive LD across ~0.45 Mb. Due to the LD structure there are > 4000 CCVs at this locus, making identification of a causal variant and its gene/s targets difficult. Of note, these CCVs are eQTLs (Supplementary Table 11) for 21 coding and non-coding genes in cortical tissue, including *CRHR1*[87] (FDR P_{CMC} = 0.009) and other genes known to be involved in brain development such as Wnt Family Member 3 (*WNT3*: FDR P_{CMC} = 0.009), Microtuble Associated Protein Tau (*MAPT*[88]: FDR P_{CMC} = 0.009) and KAT8 Regulatory NSL Complex Subunit 1 (*KANSL1*[89]: FDR P_{CMC} = 0.009) (Supplementary Table 11). Of the CCVs 59 are exonic variants: 5 of these are non-synonymous variants predicted to alter the function of *MAPT* (rs12185233, rs17651549, rs63750417), *KANSL1* (rs35833914) and *SPPL2C* (rs12373123).

rs1628768, chromosome 10q24.33

Lead SNP rs1628768 is located between the coding genes 5'-Nucleotidase, Cytosolic II (*NTC52*) and Internexin Neuronal Intermediate Filament Protein Alpha (*INA*). In addition to rs1628768 there are 22 additional CCVs at this locus, one of which (rs7911488) is located within ATP Synthase Membrane Subunit DAPIT *ATP5MD/USMG5* intron 1, in a region of histone binding indicating promoter and enhancer activity in dorsolateral prefrontal cortex and fetal brain (RoadMap Epigenome tissues E073, E082 and E081; Fig. 2d). There is evidence for an eQTL effect for *USMG5* and a number of additional genes in various non-brain tissues (Supplementary Table 11), while in cortical tissue these CCVs are eQTLs for *INA*, encoding the fourth subunit of neuronal filaments in the adult central nervous system[89], *C10orf32*, WW Domain Binding Protein 1 Like (*WBP1L*), and the schizophrenia candidate genes Arsenite Methyltransferase (*AS3MT*) and *NT5C2*[89].

rs2802295, chromosome 6q21

Lead SNP rs2802295 is located within intron 1 of the Forkhead Box O3 (*FOXO3*) gene. This SNP is a cortical eQTL for *FOXO3* and for Zinc Finger Protein 259 Pseudogene 1 (*ZNF259P1*; Supplementary Table 11). In mouse models *Foxo3* has been shown to be linked to numerous, including neuronal death and neurotoxic amyloid beta peptide processing in an Alzheimer's model[90]).

rs34464850, chromosome 3q23

Lead SNP rs34464850 is located within intron 4 of the Transcription Factor Dp-2 (*TFDP2*) gene. This SNP is an eQTL for ATPase Na+/K+ Transporting Subunit Beta 3 (*ATP1B3*), G Protein-Coupled Receptor Kinase 7 (*GRK7*) and *TFDP2* in whole blood (Supplementary Table 11).

rs190958130, chromosome 6q22.32

Eleven significant associations with various phenotypes were identified across the 6q22.32 region (Supplementary Table 10), comprising three independent genomic loci (r^2 < 0.25, Supplementary Table 10). Lead SNP rs190958130 is a low frequency variant (minor allele frequency (MAF) ~ 0.4)

located between the Centromere Protein W (*CENPW*) and R-Spondin 3 (*RSPO3*) genes. This SNP is in very close proximity but low LD to a higher frequency SNP, rs4273712 (MAF ~ 0.37, $R^2_{rs190958130\text{-}rs4273712} = 0.011$), associated with total, caudal middle frontal and parahippocampal SA in this study, and also previously associated with intracranial volume. *CENPW* is an interesting candidate as while a direct link between this gene and cortical development has not been reported, many other centrosomal proteins have been implicated in microcephaly[91], with alterations in centrosomal proteins impacting cell proliferation and hence cortex structure.

rs190958130 and rs4273712, chromosome 6q22.32
Lead SNP rs11171739 is located between the Ribosomal Protein S26 (*RPS26*) and Erb-B2 Receptor Tyrosine Kinase 3 (*ERBB3*) genes. This low frequency SNP (MAF = 0.04) is a cortical eQTL for *RPS26* ($P_{GTEX\ Brain\ cortex} = 7.4 \times 10^{-44}$), *ERBB3* (FDR $P_{CMC} = 0.009$) and for Sulfite Oxidase (*SUOX*; $P_{GTEX\ Brain\ cortex} = 5.5 \times 10^{-8}$). In mice, Erbb3 has been shown to bind Erbb4, essential for neuronal survival[92]. *SUOX* mutations are responsible for Isolated Sulphite Oxidase Deficiency, a neurometabolic disease with multiple neurological findings including substantial neuronal loss[93].

Lead SNP rs4273712 is also located between *CENPW* and *RSPO3* genes, although there is no LD between this common SNP and the lower frequency variant rs190958130. Proxy SNPs for rs4273712, along with other SNPs in the region associated with various other phenotypes (rs2184968 and rs9401907, pairwise r^2 between these SNPs ≤ 0.25; Supplementary Table 10), are cortical eQTLs for the TRNA Methyltransferase 11 Homolog (*TRMT11*: FDR $P_{CMC} = 0.049$) gene. This SNP was previously associated with intracranial volume[15].

Loci associated with Average Thickness:
rs630934, chromosome 3p22.1
Lead SNP rs630934 is located between the Ribosomal Protein SA (*RPSA*) and Myelin-Associated Oligodendroctye Basic Protein (*MOBP*) genes. *MOBP* is an interesting candidate gene for cortical thickness due to its role in myelination, and that expression is higher post- than pre-natally (Fig. 2f). However, an eQTL association with *MOBP* is seen only in GTEx tibial nerve tissue, with more extensive eQTL associations seen for other nearby genes, particularly *RPSA*, in other tissue types (Supplementary Table 11). *RPSA*, with functions as a ribosomal protein and a non-integrin laminin receptor, has been shown to have a role in neuronal migration through a functional interaction with *ZNF804A*[94]. There are no chromatin interactions or cortical eQTLs associated with rs630934 or its proxies in cortical data currently available in the FUMA database.

rs11692435, chromosome 2q11.2
Lead SNP rs11692435 is located within exon ARP1 Actin Related Protein 1 Homolog B (*ACTR1B*) gene. While there are other CCVs at this locus, rs11692435 is itself an interesting candidate causal SNP as it causes an amino acid replacement predicted to be 'damaging' to protein function by SIFT and 'probably damaging' by PolyPhen (http://www.snp-nexus.org/; Supplementary Table 10). This SNP and its proxies are eQTLs for *ACTR1B* and for other nearby genes in numerous tissues (Supplementary Table 11).

Regional Associations:
rs1080066, chromosome 15q14 (precentral SA, rostral middle frontal SA)
Located within intron 1 of lincRNA *RP11-624L4.1* and flanked by coding genes RA Guanyl Releasting Protein 1 (*RASGRP1*) and Thrombospondin 1 (*THBS1*), lead SNP rs1080066 was the most significant association (with precentral SA) detected across all of our phenotypes. Another four SNPs in very high LD with rs1080066 were associated with six additional SA and TH phenotypes. A sixth SNP, rs4923822 located ~22 Kb downstream and associated with transverse temporal SA, is in moderate LD (r^2 ~0.39 in Europeans) to the other five SNPs comprising this independent genomic locus (Supplementary Table 10).

Accross the six lead SNPs overlapping CCV sets include up to 14 SNPs, although this can be reduced to a minimum set of 10 that includes all six lead SNPs. This minimal set is indicated as influencing the expression of *THBS1*, and a non-coding RNA co-located with *THBS1* exons 18 and 19 (CTD-2033D15.1), in whole blood (Supplementary Table 11). These CCVs are located in a chromosomal region that interacts with downstream regions housing the promoters of *RP11-624L4.1* and *THBS1* in neural progenitor cells (Fig 4a; Supplementary Table 11). *THBS1* is also implicated as a candidate gene for two (lead SNPs rs3862145 [postcentral SA] and rs78502100 [supramarginal SA]) of the additional five independent genomic loci in this cytoband, through chromatin interactions between chromosomal regions housing these SNPs and the *THBS1* promoter in neural progenitor cells (Supplementary Table 11). *THBS1* has a role in synaptogenesis and the maintenance of synaptic integrity[95].

rs73313052, chromosome 14q23.1 (precuneus, pericalcarine and cuneus SA)
Lead SNP rs73313052 is one of five SNPs associated with six phenotypes at this independent genomic locus (Supplementary Table 10). These SNPs are located between the coding genes Dishevelled Binding Antagonist of Beta Catenin 1 (*DACT1*), with a role in synapse development[39], and Dishevelled Associated Activator of Morphogenesis 1 (*DAAM1*), recently shown to have a role in neuronal dendritic protrusion morphology[96]. There are two additional independent genomic loci located in this cytoband (Supplementary Table 10), one centromeric to rs73313052 and upstream of *DACT1* (most significant SNP rs160459, middle temporal TH) and one telomeric and at the 3' end of *DAAM1* (most significant SNP rs17834032, fusiform SA). Within each locus LD between SNPs is high ($r^2 > 0.8$), but there is no LD ($r^2 = 0$) between SNPs comprising the different loci.

Across all three genomic loci there is evidence for an influence on *DAAM1*. The locus represented by rs73313052 is located in the *DAAM1* promoter region (upstream and including *DAAM1* intron 1; Fig 4e), with SNPs here acting as cortical eQTLs for *DAAM1* (e.g. rs73313052 FDR $P_{CMC} = 0.049$) and the nearby genes G Protein-Coupled Receptor 135 (*GPR135*) and Trans-L-3-Hydroxyproline Dehydratase (L3HYPDH). Both of the other loci in this cytoband show chromatin interactions from the regions of the lead SNPs to that of the *DAAM1* promoter in neural progenitor cells, with SNPs from the locus represented by rs17834032 also acting as cortical eQTLs for *DAAM1*, *GPR135* and *L3HYPDH*. High LD proxies are located within an active transcription start site in adult cortex and fetal brain tissue (Fig. 4e).

rs910697 and rs2999158, chromosome 1p13.2
Lead SNPs rs910697 (lingual SA) and rs2999158 (pericalcarine SA) are in moderate LD with each other ($r^2 = 0.57$), and comprise independent genomic locus 9 (Supplementary Table 10). These SNPs and their proxies are cortical eQTLs for Wnt pathway genes Suppression Of Tumorigenicity 7 Like (*ST7L*) and Wnt Family Member 2B (*WNT2BI:* FDR $P_{CMC} = 0.009$ for both SNPs for both genes), in addition to Capping Actin Protein Of Muscle Z-Line Subunit Alpha 1 (*CAPZA1*: $P_{GTEx\ Brain\ cortex} = 1.7 \times 10^{-5}$) and the non-coding RNA RP4-671G15.2 ($P_{GTEx\ Brain\ cortex} = 7.1 \times 10^{-9}$).

rs11161942 and rs1413536, chromosome 1p22.2
These two lead SNPs represent independent loci ($r^2 = 0$) associated with the SA of the posterior cingulate (rs11161942) and inferior parietal (rs1413536). A third independent locus within this chromosomal region (rs59373415) is associated with the SA of the precuneus (Supplementary Table 5). All are of interest due to their proximity to and predicted functional influence on the LIM Domain Only 4 (*LMO4*) gene (Supplementary Table 11). rs1413536 and 15 additional CCVs are cortical eQTLs for *LMO4* (FDR $P_{CMC} = 0.009$), with chromatin interactions between the region housing these SNPs and the *LMO4* promoter (Supplementary Table 11).

rs6505147, chromosome 17q11.2
Lead SNP rs6505147 is associated with the SA of the insula. Located within a large block of LD spanning ~680 Kb, this SNP is of interest due to its proximity to the serotonin transporter *SLC6A4*, located at the telomeric end of the LD block. Due to the extensive LD there are an additional 276 CCVs at this locus, hence determining a causal SNP at this locus will be challenging. rs6505147 and its proxies are eQTLs for numerous genes across the region in cortical tissue (Coronin *(CORO6)*, Slingshot Protein Phosphatase 2 *(SSH2)*, EF-Hand Calcium Binding Domain 5 *(EFCAB5)*, Bleomycin Hydrolase *(BLMH)*, Golgi SNAP Receptor Complex Member 1 *(GOSR1)*, SUZ12P1 PRS4 Recombination Region *(SUZ12P))*, with evidence for promoter activity particularly in the region of the *SSH2*, *EFCAB5* and *BLMH* promoters (Fig 4h). Evidence for a role for *SLC6A4* in insula SA is less convincing, with little evidence of promoter activity or transcription in adult cortex, fetal brain or astrocytes (Fig 4h). There are, however, chromatin interactions to the region of the *SLC6A4* promoter observed in neural progenitor cells, and rs6505147 and its proxies are eQTLs for *SLC6A4* in other tissue types (whole blood, esophagus, tibial nerve and testis, Supplementary Table 11). *SLC6A4* is an obvious candidate gene at this locus that has been extensively studied in relation to behavioural traits. Concomitant with a proposed role in mental health issues associated with stress, 5-HTT knockout mice show behavioural and cortical morphological abnormalities that alter their responses to trauma and stress[97]. However, a recent meta-analysis of 31 human studies, including 38 802 individuals of European ancestry, found no clear association between depression, stress and 5-HTTLPR[42]. As for all other loci, determining the candidate SNP and the gene it influences will require further bioinformatic and functional laboratory work.

Sulcal development
Positive genetic correlations between the SA of neighbouring 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 labelled across many cortical atlases as the regions directly anterior and posterior to the central sulcus (which appears early in development[98]). 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 for SA, but not TH, of regions that directly surround them. 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.

The Desikan-Killiany atlas
The Desikan-Killiany atlas[12] used here to define the 34 regions of interest is one of many possible atlases. 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)[99]. It is possible that positive correlations between adjacent structures may reflect suboptimal partitioning of the cortex by the Desikan-Killiany atlas into distinct functional brain regions; 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 the *intraparietal* labels. Portions of these genetically correlated regions may in future be re-assigned based on other advanced imaging data, such as multimodal myelin mapping, which may better define cortical cellular architecture.

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Additional cohort information

ADNI

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative database. The ADNI was launched in 2003 as a 5-year public–private partnership to assess and optimize biomarkers for clinical trials in Alzheimer's disease. 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.

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 Supplementary Tables 2–4.

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;

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A.B., A.d.B., A.F.M., A.J., A.J.H., A.K., A.K.H., A.L.G., A.M.D., A.N.H., A.P., A.R.H., A.R.K., A.U., B.A.M., B.-C.H., B.D., B.Pi., B.W., B.W.J.H.P., C.B., C.D.W., C.J., C.L.B., C.L.Y., C.M., C.R.J., C.S.Re., D.Am., D.C.G., D.Gr., D.H.M., D.J., D.J.H., D.J.V., D.M.C., D.P.O., D.R.W., D.S.O., D.T.-G., D.v.E., D.v.R., D.Z., E.A., E.B.Q., E.J.C.d.G., E.L.H., E.Sh., G.B.P., G.D., G.F., G.I.d.Z., G.L.C., G.R., G.S., H.V., H.Y., I.A., I.E.Som., J.A.T., J.E.C., J.E.N., J.K.B., J.-L.M., J.-L.M., J.L.R., J.M.F., J.M.W., J.N.T., J.R., J.T.V., K.D., K.K., K.L.M., K.O.L., K.S., L.M.R., L.R., L.T.W., M.B.H., M.E.B., M.Fu., M.H.J.H., M.Ho., M.-J.v.T., M.J.W., M.-L.P.M., N.E.M.v.H., N.H., N.J.A.v.d.W., N.K.H., N.O., O.G., P.A.G., P.G.S., P.K., P.N., P.S.S., R.A.O., R.B., R.H., R.L.B., R.L.G., R.R., R.S.K., R.W., S.A., S.C.M., S.Ca., S.Er., S.Ko., S.M., S.M.S., T.G.M.v.E., T.R.M., T.Wh., T.W.M., U.D., V.C., V.S.M., W.D.H., W.H., W.W., X.C.

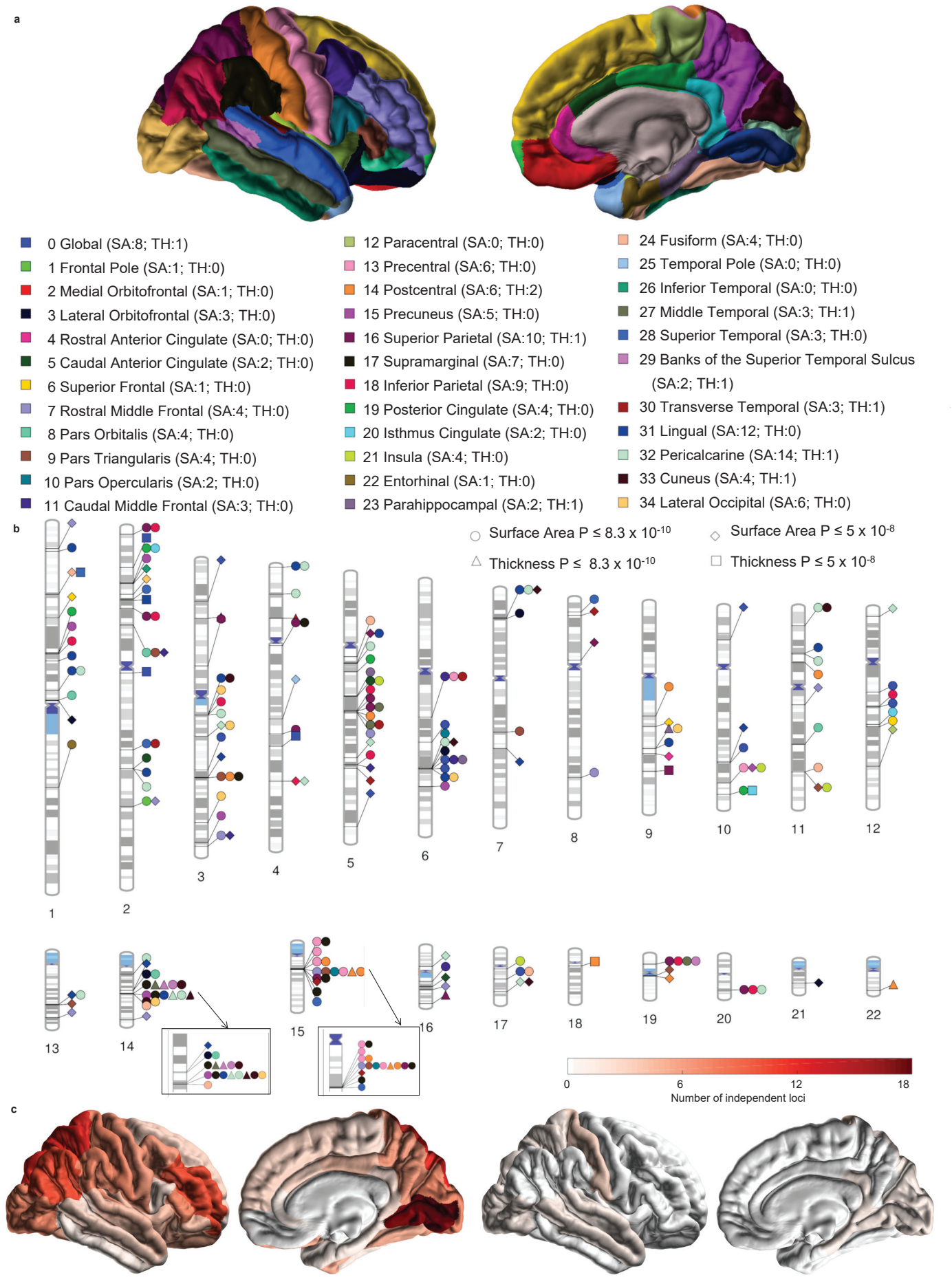
Imaging Data Analysis
A.F.M., A.H.Z., A.J.H., A.J.S., A.L.G., A.M.D., A.R., A.R.K., A.S., A.Th., A.U., B.A.G., B.C.R., B.K., B.S.P., C.B., C.C.F., C.C.H., C.D.W., C.J., C.L.Y., C.R.K.C., C.S.Ro., D.Al., D.C.G., D.Gr., D.H., D.J., D.J.H., D.M.C., D.P.H., D.P.O., D.T.-G., D.v.d.M., D.v.E., D.v.R., D.Z., E.E.L.B., E.Sh., E.Sp., E.W., F.M.R., F.P., F.S., G.I.d.Z., G.R., H.J.G., I.A., I.E.Som., I.K.A., J.A.T., J.B.J.K., J.C.V.M., J.-L.M., J.L.R., J.L.S., J.M.W., J.R., J.Z., K.D., K.L.M., K.N., K.S., K.W., L.B.L., L.H., L.Sa., L.Sc., L.Sh., L.T.S., L.T.W., L.v.E., L.Z., M.A., M.A.H., M.B.H., M.C., M.E.B., M.Fu., M.Ho., M.-J.v.T., M.J.W., M.Ki., M.P.Z., N.E.M.v.H., N.J., N.O., N.T.D., O.G., P.G.S., P.K., P.M.T., P.N., R.B., R.K., R.L.G., R.M.B., R.R., R.R.-S., S.A., S.Ca., S.Des., S.Eh., S.Er., S.F.F., S.I.T., S.Ka., S.Ke., S.L.R., S.M.C.d.Z., S.R.M., T.A., T.A.L., T.G., T.G.M.v.E., T.J., T.K., T.L.P., T.P.G., T.R.M., T.Wh., T.Wo., T.W.M., U.D., W.W., X.C., Z.Z.

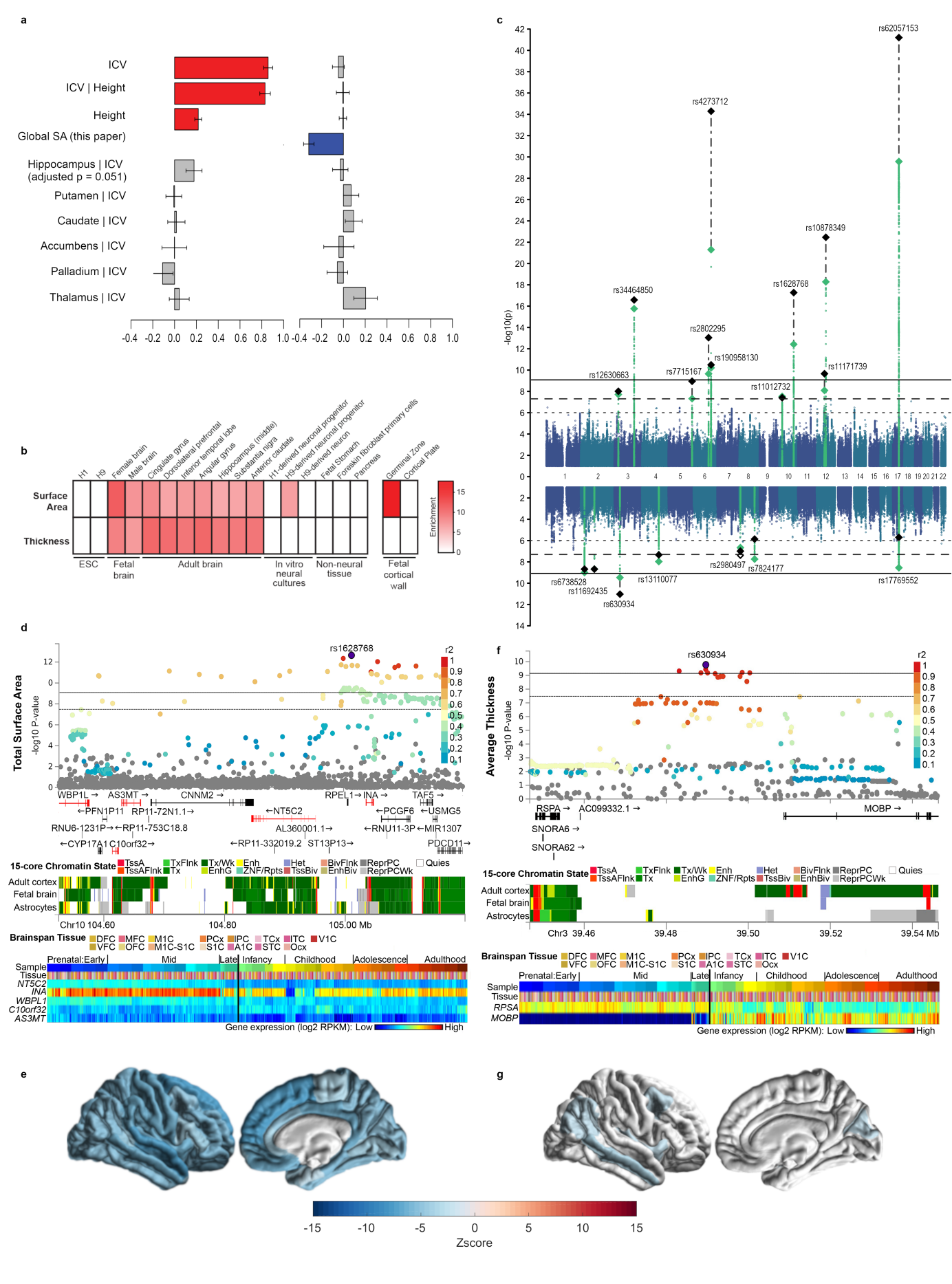
Genetic Data Collection
A.A.A., A.A.-K., A.d.B., A.J.F., A.J.H., A.J.S., A.K.H., A.M.D., A.P., A.R.H., A.R.K., B.-C.H., B.T.B., B.W., B.W.J.H.P., C.B., C.D.W., C.F., C.M., C.P.D., C.S.Re., D.C.G., D.H.M., D.R.W.,

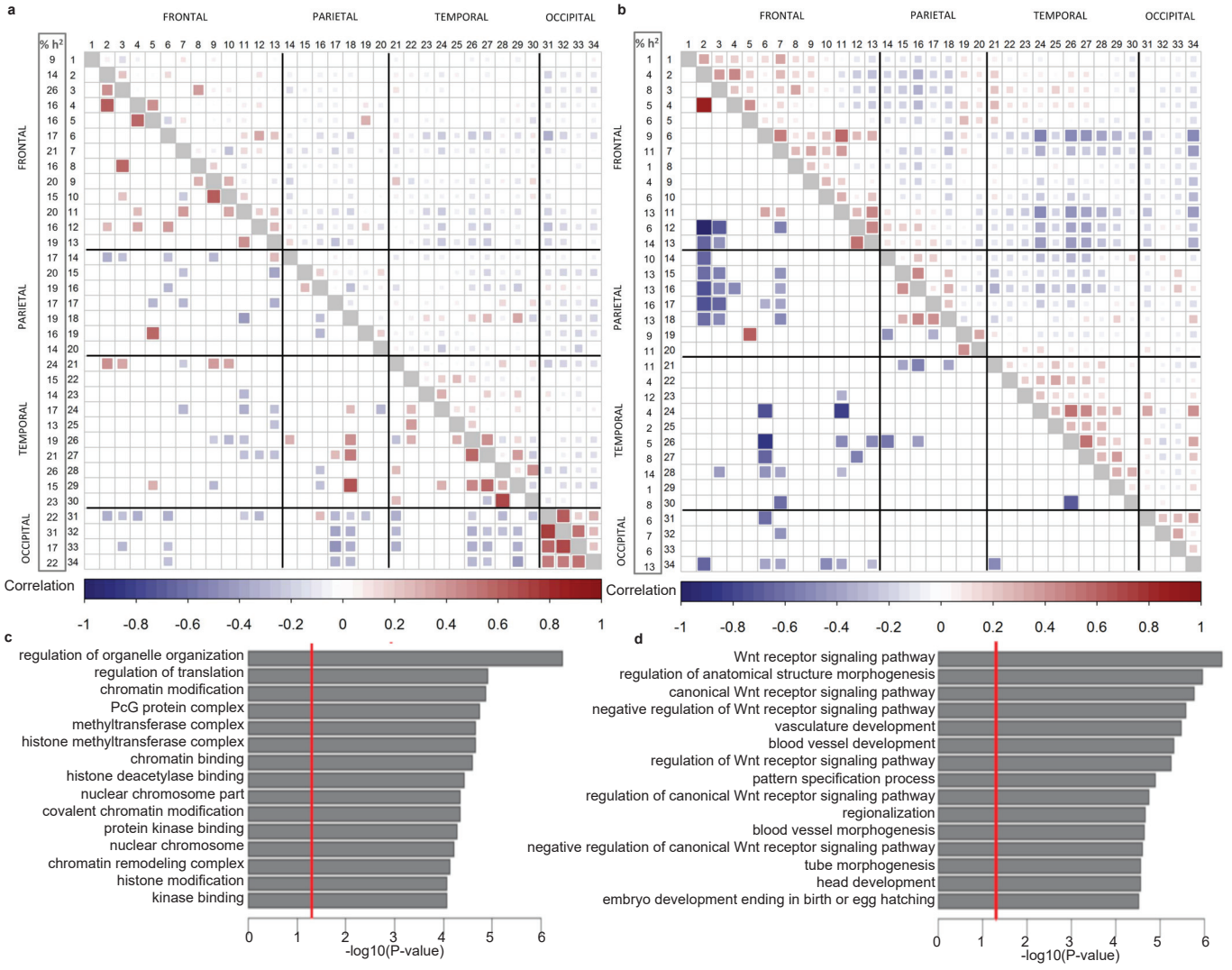
D.W.M., D.Z., E.A., E.B.Q., E.G.J., E.J.C.d.G., E.L.H., F.D., F.M., F.R.T., G.D., G.E.D., G.F., G.H., G.L.C., G.S., H.V., H.Y., I.E.Som., I.L.-C., J.A.T., J.B.J.K., J.Bl., J.E.C., J.E.N., J.-J.H., J.J.L., J.K.B., J.-L.M., J.-L.M., J.L.R., J.M.F., J.R., J.W.S., K.A.M., K.D., K.O.L., K.S., L.M.R., L.R., L.Sh., M.A.K., M.H.J.H., M.Ha., M.Ho., M.J.W., M.-L.P.M., M.M.N., M.N., N.E.M.v.H., N.G.M., N.J.A.v.d.W., N.K.H., N.O., O.G., P.K., P.R.S., P.S.S., R.A.O., R.C.G., R.H., R.L.B., R.R., R.Se., R.S.K., R.W., S.A., S.Ci., S.Dj., S.E.F., S.Eh., S.Er., S.L.H., S.M.S., T.G.M.v.E., T.J.A., T.K.d.A., T.L.P., T.W.M., U.D., V.C., V.M.S., X.C.

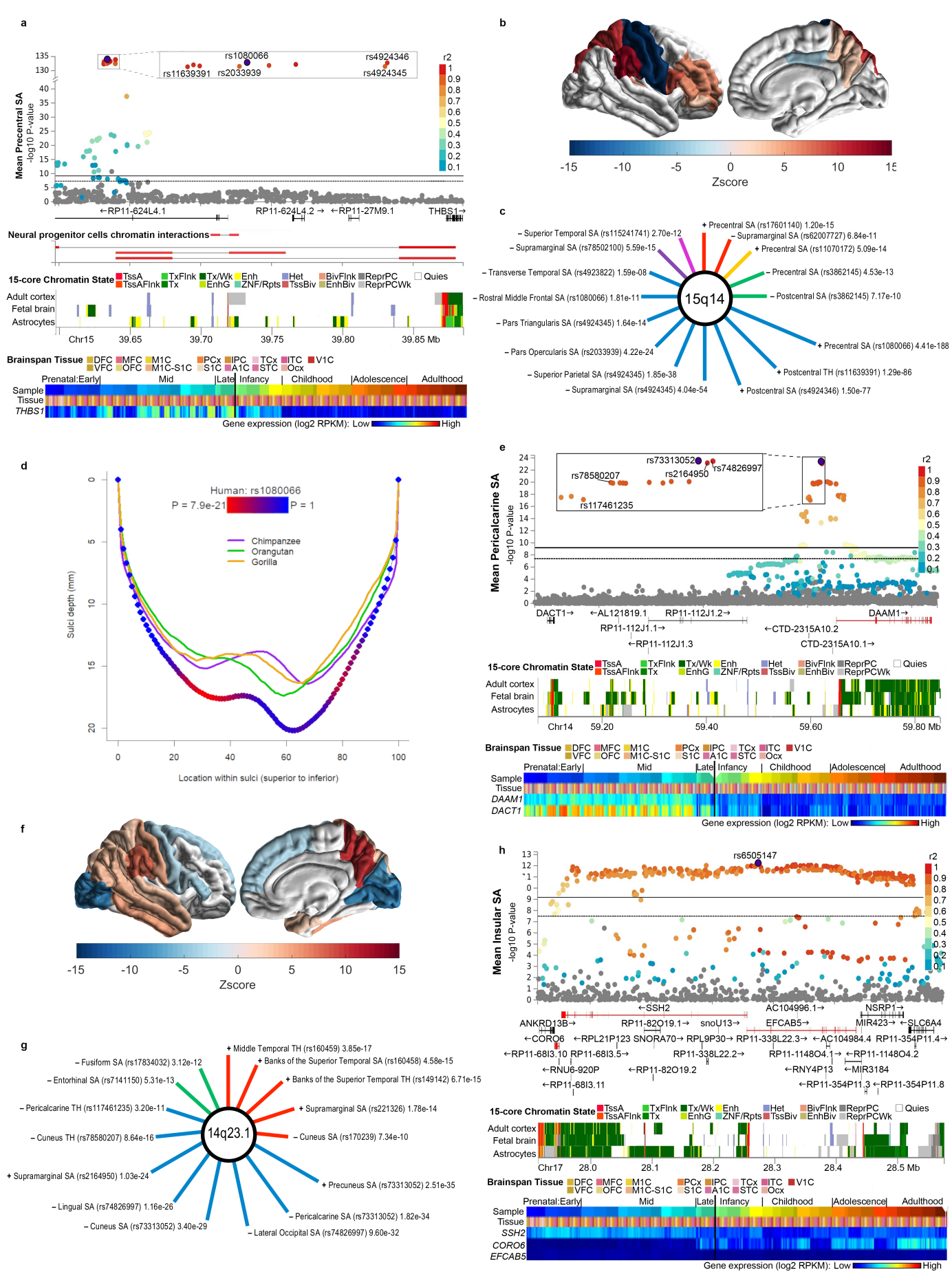
Genetic Data Analysis
A.A.-K., A.J.F., A.J.H., A.J.S., A.M.D., A.R.K., A.Te., A.Th., B.C.-D., B.K., B.M.-M., B.Pü., B.S.P., B.T.B., C.C.F., C.D.W., C.L.V., C.S.Re., C.S.Ro., C.W., C.Y.S., D.C.G., D.K., D.P.H., D.v.d.M., D.v.E., E.G.J., E.L.H., E.V., E.W., F.M., H.-R.E., I.E.J., I.E.Som., I.E.Søn., I.L.-C., I.O.F., J.Bl., J.Br., J.F.P., J.H.V., J.-J.H., J.L.R., J.L.S., J.N.P., J.S., J.W.C., J.W.S., K.E.T., K.L.G., K.N., L.C.-C., L.M.O.L., L.Sh., L.Z., M.A.A.A., M.B., M.E.G., M.Fu., M.Ha., M.I., M.J., M.J.W., M.Ki., M.Kl., M.Kn., M.L., M.M.J.v.D., N.A.G., N.G.M., N.J., N.J.A., N.K.H., N.M.-S., N.R.M., O.G., P.A.L., P.G.S., P.H.L., P.K., P.M.T., P.R.S., Q.C., R.A.O., R.M.B., R.R., R.Se., S.Da., S.Des., S.E.M., S.Eh., S.G., S.H.W., S.L.H., S.M.C.d.Z., S.N., S.R.M., T.A.L., T.G., T.G.M.v.E., T.J., T.K.d.A., T.M.L., Y.M., Y.W.

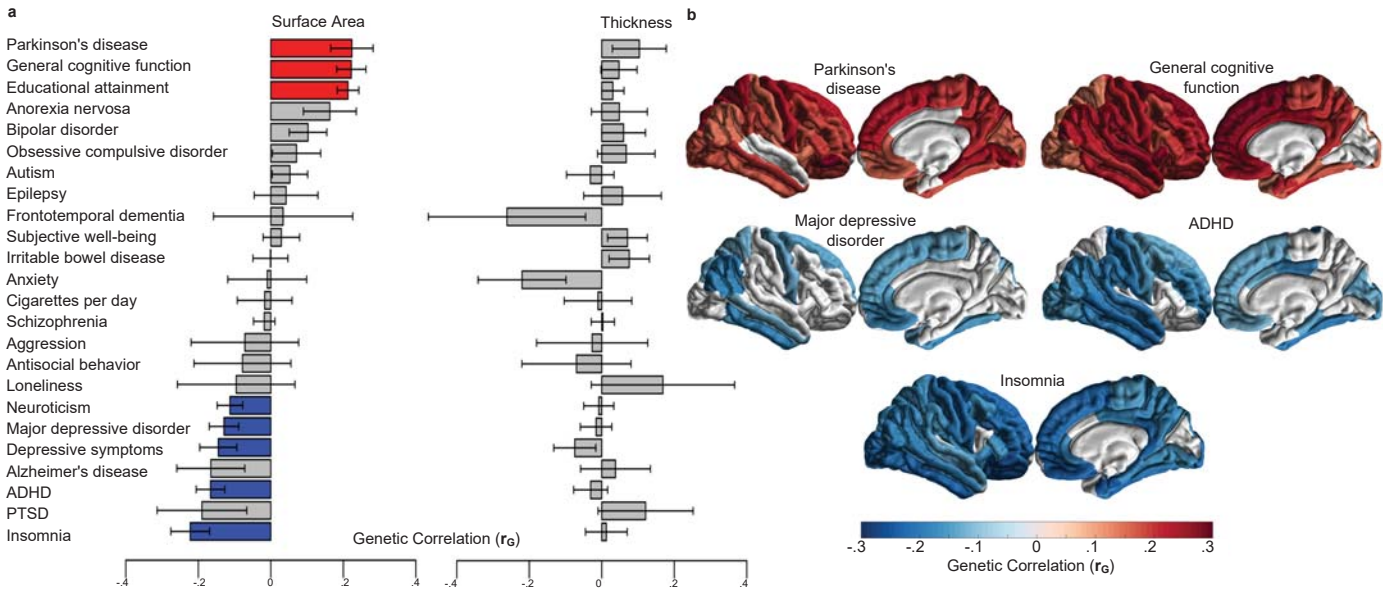
CHARGE Study Design
B.M., C.Dec., C.L.S., E.H., G.V.R., H.H.H.A., H.J.G., J.C.B., L.J.L., M.A.I., M.Fo., O.L.L., Q.Y., R.Sc., S.Deb., S.S., T.H.M., V.G., W.T.L.


a
0 Global (SA:8; TH:1)
1 Frontal Pole (SA:1; TH:0)
2 Medial Orbitofrontal (SA:1; TH:0)
3 Lateral Orbitofrontal (SA:3; TH:0)
4 Rostral Anterior Cingulate (SA:0; TH:0)
5 Caudal Anterior Cingulate (SA:2; TH:0)
6 Superior Frontal (SA:1; TH:0)
7 Rostral Middle Frontal (SA:4; TH:0)
8 Pars Orbitalis (SA:4; TH:0)
9 Pars Triangularis (SA:4; TH:0)
10 Pars Opercularis (SA:2; TH:0)
11 Caudal Middle Frontal (SA:3; TH:0)
12 Paracentral (SA:0; TH:0)
13 Precentral (SA:6; TH:0)
14 Postcentral (SA:6; TH:2)
15 Precuneus (SA:5; TH:0)
16 Superior Parietal (SA:10; TH:1)
17 Supramarginal (SA:7; TH:0)
18 Inferior Parietal (SA:9; TH:0)
19 Posterior Cingulate (SA:4; TH:0)
20 Isthmus Cingulate (SA:2; TH:0)
21 Insula (SA:4; TH:0)
22 Entorhinal (SA:1; TH:0)
23 Parahippocampal (SA:2; TH:1)
24 Fusiform (SA:4; TH:0)
25 Temporal Pole (SA:0; TH:0)
26 Inferior Temporal (SA:0; TH:0)
27 Middle Temporal (SA:3; TH:1)
28 Superior Temporal (SA:3; TH:0)
29 Banks of the Superior Temporal Sulcus (SA:2; TH:1)
30 Transverse Temporal (SA:3; TH:1)
31 Lingual (SA:12; TH:0)
32 Pericalcarine (SA:14; TH:1)
33 Cuneus (SA:4; TH:1)
34 Lateral Occipital (SA:6; TH:0)
b
Surface Area P ≤ 8.3 x 10-10
Surface Area P ≤ 5 x 10-8
Thickness P ≤ 8.3 x 10-10
Thickness P ≤ 5 x 10-8
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
0
6
12
18
Number of independent loci
c


a
ICV
ICV | Height
Height
Global SA (this paper)
Hippocampus | ICV (adjusted p = 0.051)
Putamen | ICV
Caudate | ICV
Accumbens | ICV
Palladium | ICV
Thalamus | ICV
-0.4 -0.2 0.0 0.2 0.4 0.6 0.8 1.0
b
H1
H9
Female brain
Male brain
Cingulate gyrus
Dorsolateral prefrontal
Inferior temporal lobe
Angular gyrus
Hippocampus (middle)
Substantia nigra
Anterior caudate
H1-derived neuronal progenitor
H9-derived neuronal progenitor
H9-derived neuron
Fetal Stomach
Foreskin fibroblast primary cells
Pancreas
Germinal Zone
Cortical Plate
Surface Area
Thickness
Enrichment
ESC
Fetal brain
Adult brain
In vitro neural cultures
Non-neural tissue
Fetal cortical wall
c
-log10(p)
rs62057153
rs4273712
rs10878349
rs34464850
rs1628768
rs2802295
rs190958130
rs12630663
rs7715167
rs11171739
rs11012732
rs2980497
rs7824177
rs6738528
rs11692435
rs13110077
rs630934
rs17769552
d
Total Surface Area
-log10 P-value
rs1628768
r2
WBP1L
AS3MT
CNNM2
RPEL1
INA
TAF5
PFN1P11
RP11-72N1.1
NT5C2
PCGF6
USMG5
RNU6-1231P
RP11-753C18.8
AL360001.1
RNU11-3P
MIR1307
CYP17A1
C10orf32
RP11-332019.2
ST13P13
PDCD11
15-core Chromatin State
TssA
TxFlnk
Tx/Wk
Enh
Het
BivFlnk
ReprPC
Quies
TssAFlnk
Tx
EnhG
ZNF/Rpts
TssBiv
EnhBiv
ReprPCWk
Adult cortex
Fetal brain
Astrocytes
Chr10 104.60
104.80
105.00 Mb
Brainspan Tissue
DFC
MFC
M1C
PCx
IPC
TCx
ITC
V1C
VFC
OFC
M1C-S1C
S1C
A1C
STC
Ocx
Prenatal:Early
Mid
Late
Infancy
Childhood
Adolescence
Adulthood
Sample
Tissue
NT5C2
INA
WBPL1
C10orf32
AS3MT
Gene expression (log2 RPKM): Low
High
f
Average Thickness
-log10 P-value
rs630934
r2
RSPA
AC099332.1
MOBP
SNORA6
SNORA62
Chr3 39.46
39.48
39.50
39.52
39.54 Mb
RPSA
MOBP
e
g
-15
-10
-5
0
5
10
15
Zscore


a
FRONTAL
PARIETAL
TEMPORAL
OCCIPITAL
% h²
Correlation
-1 -0.8 -0.6 -0.4 -0.2 0 0.2 0.4 0.6 0.8 1
b
FRONTAL
PARIETAL
TEMPORAL
OCCIPITAL
% h²
Correlation
-1 -0.8 -0.6 -0.4 -0.2 0 0.2 0.4 0.6 0.8 1
c
regulation of organelle organization
regulation of translation
chromatin modification
PcG protein complex
methyltransferase complex
histone methyltransferase complex
chromatin binding
histone deacetylase binding
nuclear chromosome part
covalent chromatin modification
protein kinase binding
nuclear chromosome
chromatin remodeling complex
histone modification
kinase binding
0 1 2 3 4 5 6
-log10(P-value)
d
Wnt receptor signaling pathway
regulation of anatomical structure morphogenesis
canonical Wnt receptor signaling pathway
negative regulation of Wnt receptor signaling pathway
vasculature development
blood vessel development
regulation of Wnt receptor signaling pathway
pattern specification process
regulation of canonical Wnt receptor signaling pathway
regionalization
blood vessel morphogenesis
negative regulation of canonical Wnt receptor signaling pathway
tube morphogenesis
head development
embryo development ending in birth or egg hatching
0 1 2 3 4 5 6
-log10(P-value)


a
Mean Precentral SA
-log10 P-value
rs1080066
rs4924346
rs11639391
rs2033939
rs4924345
r2
←RP11-624L4.1
RP11-624L4.2 →
←RP11-27M9.1
THBS1→
Neural progenitor cells chromatin interactions
15-core Chromatin State
TssA TxFlnk Tx/Wk Enh Het BivFlnk ReprPC Quies
TssAFlnk Tx EnhG ZNF/Rpts TssBiv EnhBiv ReprPCWk
Adult cortex
Fetal brain
Astrocytes
Chr15 39.65 39.70 39.75 39.80 39.85 Mb
Brainspan Tissue
DFC MFC M1C PCx IPC TCx ITC V1C
VFC OFC M1C-S1C S1C A1C STC Ocx
Prenatal:Early Mid Late Infancy Childhood Adolescence Adulthood
Sample
Tissue
THBS1
Gene expression (log2 RPKM): Low High
b
-15 -10 -5 0 5 10 15
Zscore
c
15q14
+ Precentral SA (rs17601140) 1.20e-15
– Superior Temporal SA (rs115241741) 2.70e-12
– Supramarginal SA (rs62007727) 6.84e-11
– Supramarginal SA (rs78502100) 5.59e-15
+ Precentral SA (rs11070172) 5.09e-14
– Transverse Temporal SA (rs4923822) 1.59e-08
– Precentral SA (rs3862145) 4.53e-13
– Rostral Middle Frontal SA (rs1080066) 1.81e-11
– Postcentral SA (rs3862145) 7.17e-10
– Pars Triangularis SA (rs4924345) 1.64e-14
+ Precentral SA (rs1080066) 4.41e-188
– Pars Opercularis SA (rs2033939) 4.22e-24
+ Postcentral TH (rs11639391) 1.29e-86
– Superior Parietal SA (rs4924345) 1.85e-38
– Supramarginal SA (rs4924345) 4.04e-54
+ Postcentral SA (rs4924346) 1.50e-77
d
Human: rs1080066
P = 7.9e-21
P = 1
Chimpanzee
Orangutan
Gorilla
Sulci depth (mm)
Location within sulci (superior to inferior)
e
Mean Pericalcarine SA
-log10 P-value
rs73313052
rs74826997
rs78580207
rs2164950
rs117461235
r2
DACT1→
←AL121819.1
RP11-112J1.2→
DAAM1→
RP11-112J1.1→
←CTD-2315A10.2
←RP11-112J1.3
CTD-2315A10.1→
15-core Chromatin State
Adult cortex
Fetal brain
Astrocytes
Chr14 59.20 59.40 59.60 59.80 Mb
Brainspan Tissue
Prenatal:Early Mid Late Infancy Childhood Adolescence Adulthood
Sample
Tissue
DAAM1
DACT1
Gene expression (log2 RPKM): Low High
f
-15 -10 -5 0 5 10 15
Zscore
g
14q23.1
+ Middle Temporal TH (rs160459) 3.85e-17
– Fusiform SA (rs17834032) 3.12e-12
+ Banks of the Superior Temporal SA (rs160458) 4.58e-15
– Entorhinal SA (rs7141150) 5.31e-13
+ Banks of the Superior Temporal TH (rs149142) 6.71e-15
– Pericalcarine TH (rs117461235) 3.20e-11
+ Supramarginal SA (rs221326) 1.78e-14
– Cuneus TH (rs78580207) 8.64e-16
– Cuneus SA (rs170239) 7.34e-10
+ Supramarginal SA (rs2164950) 1.03e-24
+ Precuneus SA (rs73313052) 2.51e-35
– Lingual SA (rs74826997) 1.16e-26
– Pericalcarine SA (rs73313052) 1.82e-34
– Cuneus SA (rs73313052) 3.40e-29
– Lateral Occipital SA (rs74826997) 9.60e-32
h
Mean Insular SA
-log10 P-value
rs6505147
r2
←SSH2
AC104996.1→
NSRP1→
ANKRD13B→
RP11-82O19.1→
snoU13→
EFCAB5→
MIR423→
←SLC6A4
←CORO6
←RPL21P123
SNORA70→
RPL9P30→
RP11-338L22.3→
←AC104984.4
RP11-354P11.4→
←RP11-68I3.10
RP11-68I3.5→
RP11-338L22.2→
RP11-1148O4.1→
←RP11-1148O4.2
←RNU6-920P
←RP11-82O19.2
←RNY4P13
←MIR3184
←RP11-68I3.11
←RP11-354P11.3
←RP11-354P11.8
15-core Chromatin State
Adult cortex
Fetal brain
Astrocytes
Chr17 28.0 28.1 28.2 28.3 28.4 28.5 Mb
Brainspan Tissue
Prenatal:Early Mid Late Infancy Childhood Adolescence Adulthood
Sample
Tissue
SSH2
CORO6
EFCAB5
Gene expression (log2 RPKM): Low High


a
Surface Area
Thickness
Parkinson's disease
General cognitive function
Educational attainment
Anorexia nervosa
Bipolar disorder
Obsessive compulsive disorder
Autism
Epilepsy
Frontotemporal dementia
Subjective well-being
Irritable bowel disease
Anxiety
Cigarettes per day
Schizophrenia
Aggression
Antisocial behavior
Loneliness
Neuroticism
Major depressive disorder
Depressive symptoms
Alzheimer's disease
ADHD
PTSD
Insomnia
Genetic Correlation (r_G)
-.4
-.2
0
.2
.4
b
Parkinson's disease
General cognitive function
Major depressive disorder
ADHD
Insomnia
-.3
-.2
-.1
0
.1
.2
.3
Genetic Correlation (r_G)