Cortical thickness, surface area and volumes vary with age and cognitive function, and in neurological and psychiatric diseases. Here we report heritability, genetic correlations and genome-wide associations of these cortical measures across the whole cortex, and in 34 anatomically predefined regions. Our discovery sample comprises 22,824 individuals from 20 cohorts within the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium and the UK Biobank. We identify genetic heterogeneity between cortical measures and brain regions, and 160 genome-wide significant associations pointing to wnt/β-catenin, TGF-β and sonic hedgehog pathways. There is enrichment for genes involved in anthropometric traits, hindbrain development, vascular and neurodegenerative disease and psychiatric conditions. These data are a rich resource for studies of the biological mechanisms behind cortical development and aging.
The cortex is the largest part of the human brain, associated with higher brain functions, such as perception, thought, and action. Brain cortical thickness (CTh), cortical surface area (CSA), and cortical volume (CV) are morphological markers of cortical structure obtained from magnetic resonance imaging (MRI). These measures change with age1–3 and are linked to cognitive functioning4,5. The human cortex is also vulnerable to a wide range of disease or pathologies, ranging from developmental disorders and early onset psychiatric and neurological diseases to neurodegenerative conditions manifesting late in life. Abnormalities in global or regional CTh, CSA, and CV have been observed in neurological and psychiatric disorders, such as Alzheimer’s disease5, Parkinson’s disease6, multiple sclerosis7, schizophrenia8, bipolar disorder9, depression10, and autism11. The best method to study human cortical structure during life is using brain MRI. Hence, understanding the genetic determinants of the most robust MRI cortical markers in apparently normal adults could identify pathological pathways relevant to brain development, aging, and various diseases. Neurons in the neocortex are organized in columns which run perpendicular to the surface of the cerebral cortex12; and, according to the radial unit hypothesis, CTh is determined by the number of cells within the columns and CSA is determined by the number of columns13.

Thus, CTh and CSA reflect different mechanisms in cortical development13,14 and are likely influenced by different genetic factors15–18. CV, which is the product of CTh and CSA, is determined by a combination of these two measures, but the relative contribution of CTh and CSA to CV may vary across brain regions. CTh, CSA, and CV are all strongly heritable traits15–21, with estimated heritability of 0.69–0.81 for global CTh, and from 0.42 to 0.90 for global CSA15,16,18. Across different cortical regions, however, there is substantial regional variation in heritability of CTh, CSA, and CV15–21.

Since CTh, CSA, and CV are differentially heritable and genetically heterogeneous, we explore the genetics of each of these imaging markers using genome-wide association analyses (GWAS) in large population-based samples. We study CTh, CSA, and CV in the whole cortex and in 34 cortical regions in 22,824 individuals from 21 discovery cohorts and replicate the strongest associations in 22,363 persons from the Enhancing Neuroimaging Genetics through Meta-analysis (ENIGMA) consortium. Our analyses reveal 160 genome-wide significant associations pointing to wnt/β-catenin, TGF-β, and sonic hedgehog pathways. We observe genetic heterogeneity between cortical measures and brain regions and find enrichment for genes involved in anthropometric traits, hindbrain development, vascular and neurodegenerative disease, and psychiatric conditions.

**Results**

**Genome-wide association analysis.** The analyses of global CTh, CSA, and CV included 22,163, 18,617, and 22,824 individuals, respectively. After correction for multiple testing ($p_{\text{Discovery}} < 1.09 \times 10^{-5}$), we identified no significant associations with global CTh. However, we identified 12 independent loci associated with global CSA ($n = 6$) and CV ($n = 6$). These are displayed in Supplementary Data 1 and Supplementary Figs. 1 and 2. Five of the 6 CSA loci were replicated in an external (ENIGMA consortium) sample.22 The ENIGMA consortium only analyzed CSA and CTh.

GWAS of CTh, CSA, and CV in 34 cortical regions of interest (ROIs) identified 148 significant associations. There were 16 independent loci across 8 chromosomes determining CTh of 9 regions (Supplementary Data 2), 54 loci across 16 chromosomes associated with CSA of 21 regions (Supplementary Data 3), and 78 loci across 17 chromosomes determining CV of 23 cortical regions (Supplementary Data 4). We replicated 57 out of 64 regional CTh and CSA loci that were available in the ENIGMA consortium sample22 using a conservative replication threshold of $p_{\text{Replication}} = 3.1 \times 10^{-4}$, 0.05/160. Region-specific variants with the strongest association at each genomic locus are shown in Tables 1–3. Chromosomal ideograms showing genome-wide significant associations with global and regional cortical measures in the discovery stage are presented in Fig. 1.

If we had used a more stringent threshold of $p_{\text{Discovery}} < 4.76 \times 10^{-10} = 5 \times 10^{-5}/105$, correcting for all the 105 GWAS analyses performed, we would have identified 142 significant associations (Supplementary Data 1–4).

The strongest associations with CTh and CV were observed for rs2033939 at 15q14 ($p_{\text{Discovery, CTh}} = 1.17 \times 10^{-73}$ and $p_{\text{Discovery, CV}} = 4.34 \times 10^{-133}$) in the postcentral (primary somatosensory) cortex, and for CSA with rs1080066 at 15q14 ($p_{\text{Discovery, CSA}} = 8.45 \times 10^{-199}$) in the prescentral (primary motor) cortex. Figure 2 shows the lowest p-value of each cortical region. The postcentral cortex was also the region with the largest number of independent associations, mainly at a locus on 15q14. The corresponding regional association plots are presented in Supplementary Fig. 3.

Quantile-quantile plots of all meta-analyses are presented in Supplementary Figs. 4–7 and the corresponding genomic inflation factors ($\lambda_{\text{GC}}$), LD score regression (LDSR) intercepts, and ratios are shown in Supplementary Data 5. Although we observe inflated test statistics for some traits with $\lambda_{\text{GC}}$ between 1.02 and 1.11, LDSR intercepts between 0.98 and 1.02 indicate that the inflation is mainly due to polygenicity. For traits with $\lambda_{\text{GC}} > 1.05$, the LDSR ratios range between 0.00 and 0.15 which means that a maximum of 15% of the inflation is due to other causes.

**Associations across cortical measures and with other traits.**

Supplementary Data 6 presents variants that are associated with the CSA or CV across multiple regions. We observed 25 single nucleotide polymorphisms (SNPs) that determined CTh and CV of the same region, but no SNPs that determined both the CTh and CSA of any given region (Supplementary Data 6). We replicated 57 out of 64 SNP loci that were available in the ENIGMA consortium sample using a conservative replication threshold of $p_{\text{Discovery}} < 4.76 \times 10^{-10} = 5 \times 10^{-5}/105$, correcting for all the 105 GWAS analyses performed, we would have identified 142 significant associations (Supplementary Data 1–4).

For CTh, we observed the maximum phenotypic variance explained by the PRS ($p_{\text{PRS}}^2$) in the global cortex ($p_{\text{PRS}}^2 = 0.015$, $p_{\text{PRS}} = 1.05 \times 10^{-29}$), and for CSA and CV in the pericalcarine cortex ($p_{\text{PRS}}^2 = 0.029$, $p_{\text{PRS,CSA}} = 1.29 \times 10^{-50}$, $p_{\text{PRS,CV}}^2 = 0.032$, $p_{\text{PRS,CV}} = 5.30 \times 10^{-56}$). When assessing genetic overlap with other traits, we observed that SNPs determining these cortical measures have been previously associated with anthropometric (height), neurologic (Parkinson’s disease, corticobasal degeneration, and Alzheimer’s disease), psychiatric (neuroticism and schizophrenia) and cognitive performance traits as well as with total intracranial volume (TIV) on brain MRI (Supplementary Data 10–12).

**Gene identification.** Positional mapping based on ANNOVAR showed that most of the lead SNPs were intergenic and intronic
Table 1 Genome-wide significant associations ($P_{\text{discovery}} < 1.109 \times 10^{-9}$) of regional CTh.

| Region        | Locus          | Lead SNP          | Nearest gene | Annotation | Position  | Replication | Discovery | Pooled Meta-analysis |
|---------------|----------------|-------------------|--------------|------------|-----------|-------------|-----------|---------------------|
| Superior      | 16q24.2        | rs4843227         | WNT3         | Intronic   | 87225139  | 2.45E-12    | 2.31E-05  | 5.76E-05            |
| Middle        | 17q21.31       | rs199504          | KIAA0586     | Intronic   | 44861003  | 1.17E-10    | 1.30E-10  | 1.17E-10            |
| Inferior      | 14q23.1        | rs160458          | LOC101928708 | Intergenic | 59074878  | 6.45E-08    | 6.45E-08  | 6.45E-08            |
| Superior      | 1q41           | rs10494988        | Parietal     | Intergenic | 215141570 | 3.66E-08    | 3.66E-08  | 3.66E-08            |
| Superior      | 15q14          | rs2033939         | Postcentral  | Intergenic | 39633904  | 5.18E-07    | 5.18E-07  | 5.18E-07            |
| Superior      | 14q23.1        | rs4901904         | SALL1        | Intronic   | 59624317  | 1.38E-04    | 1.38E-04  | 1.38E-04            |
| Superior      | 14q23.1        | rs4901904         | LPAR1        | Intronic   | 59624317  | 1.46E-13    | 1.46E-13  | 1.46E-13            |
| Superior      | 14q23.1        | rs3715003         | CHRNA3       | Intergenic | 4901904   | 2.62E-02    | 2.62E-02  | 2.62E-02            |
| Superior      | 14q23.1        | rs4901904         | C1orf122     | Intergenic | 4901904   | 1.45E-04    | 1.45E-04  | 1.45E-04            |

Pathway analysis. MAGMA gene set analyses identified 7 pathways for CTh, 3 pathways for CSA and 9 pathways for CV (Supplementary Data 20). Among them are the gene ontology (GO) sets hindbrain morphogenesis (strongest association with thickness of middle temporal cortex), forebrain generation of neurons (with surface area of precentral cortex), and central nervous system neuron development (with volume of transverse temporal cortex). However, after Bonferroni correction only one significant pathway ($p < 1.02 \times 10^{-7}$) remained: regulation of catabolic process for CTh of the inferior temporal cortex. InnateDB pathway analyses of genes mapped to independent lead SNPs by FUMA showed a significant overlap between CTh and CSA genes and the Wnt signaling pathway (Supplementary Figs. 8 and 9) as well as a significant overlap between CV genes and the basal cell carcinoma pathway (Supplementary Fig. 10).

Heritability. Heritability estimates ($h^2$) of global CTh were 0.64 (standard error (se) = 0.12; $p_{\text{SOLAR}} = 3 \times 10^{-7}$) in the ASPS-Fam study and 0.45 (se = 0.08; $p_{\text{GCTA}} = 2.5 \times 10^{-7}$) in the Rotterdam study (RS). For CSA, $h^2$ was 0.84 (se = 0.12; $p_{\text{SOLAR}} = 2.63 \times 10^{-11}$) in ASPS-Fam and 0.33 (se = 0.08; $p_{\text{GCTA}} = 1 \times 10^{-4}$) in RS, and for CV, $h^2$ was 0.80 (se = 0.11; $p_{\text{SOLAR}} = 1.10 \times 10^{-9}$) in ASPS-Fam and 0.32 (se = 0.08; $p_{\text{GCTA}} = 1 \times 10^{-4}$) in RS. There was a large range in heritability estimates of regional CTh, CSA, and CV (Supplementary Data 21).

Heritability based on common SNPs as estimated with LDSR was 0.25 (se = 0.03) for global CTh, 0.29 (se = 0.04) for global CSA and 0.30 (se = 0.03) for global CV. LDSR heritability estimates of regional CTh, CSA, and CV are presented in Supplementary Data 21 and Supplementary Fig. 11. For the regional analyses, the estimated heritability ranged from 0.05 to 0.18 for CTh, from 0.07 to 0.36 for CSA and from 0.06 to 0.32 for CV. Superior temporal cortex ($h^2_{\text{CTh}} = 0.18$, $h^2_{\text{CSA}} = 0.30$, $h^2_{\text{CV}} = 0.26$), precuneus ($h^2_{\text{CTh}} = 0.16$, $h^2_{\text{CSA}} = 0.29$, $h^2_{\text{CV}} = 0.28$) and pericarotidine ($h^2_{\text{CTh}} = 0.15$, $h^2_{\text{CSA}} = 0.36$, $h^2_{\text{CV}} = 0.32$) are among the most genetically determined regions.

The results of partitioned heritability analyses for global and regional CTh, CSA, and CV with functional annotation and additionally with cell-type-specific annotation are presented in (Fig. 3). One variant, rs2279829, which was associated with both CSA and CV of the pars triangularis, postcentral and supramarginal cortices, is located in the 3′UTR of ZIC4 at 3q24. We also found an exonic variant, rs10283100, in gene ENPP2 at 8q24.12 associated with CV of the insula.

We used multiple strategies beyond positional annotation to identify specific genes implicated by the various GWAS associated SNPs. FUMA identified 232 genes whose expression was determined by these variants (eQTL) and these and other genes implicated by chromatin interaction mapping are shown in Supplementary Data 13–15. MAGMA gene-based association analyses revealed 70 significantly associated ($p < 5.87 \times 10^{-8}$) genes (Supplementary Data 16–18). For global CSA and CV, 7 of 9 genes associated with each measure overlapped, but there was no overlap with global CTh. For regional CSA and CV, we found 28 genes across 13 cortical regions that determined both measures in the same region. Figure 4 summarizes the results of GTEx eQTL, chromatin interaction, positional annotation, and gene-based mapping strategies for all regions. While there are overlapping genes identified using different approaches, only DAAM1 gene (Chr14q23.1) is identified by all types of gene mapping for CV of insula. eQTL associations of our independent lead SNPs in the Religious Orders Study Memory and Aging Project (ROSMAP) dorsolateral frontal cortex gene expression dataset are presented in Supplementary Data 19.
| Lobe | Region | Locus | Position | Lead SNP | Nearest gene | Annotion | N | P (Dis) | P (Rep) | P (Pooled) |
|------|--------|-------|----------|----------|--------------|----------|---|--------|--------|-----------|
|      |        |       |          |          |              |          |   |        |        |           |
|      | Global |       |          |          |              |          |   |        |        |           |
|      |        |       |          |          |              |          |   |        |        |           |
|      | Frontal|       |          |          |              |          |   |        |        |           |
|      | Superior frontal |      |          |          |              |          |   |        |        |           |
|      | Caudal middle frontal |      |          |          |              |          |   |        |        |           |
|      | Pars opercularis |       |          |          |              |          |   |        |        |           |
|      | Pars triangularis |      |          |          |              |          |   |        |        |           |
|      | Precentral |      |          |          |              |          |   |        |        |           |
|      |       |       |          |          |              |          |   |        |        |           |
|      | Temporal |       |          |          |              |          |   |        |        |           |
|      | Superior temporal |      |          |          |              |          |   |        |        |           |
|      | Middle temporal |      |          |          |              |          |   |        |        |           |
|      | Banksts |       |          |          |              |          |   |        |        |           |
|      | Fusiform |       |          |          |              |          |   |        |        |           |
|      | Transverse temporal |      |          |          |              |          |   |        |        |           |
|      | Parietal |       |          |          |              |          |   |        |        |           |
|      | Superior parietal |      |          |          |              |          |   |        |        |           |
|      | Inferior parietal |      |          |          |              |          |   |        |        |           |
|      | Supramarginal |      |          |          |              |          |   |        |        |           |
|      | Postcentral |      |          |          |              |          |   |        |        |           |
|      | Precuneus |      |          |          |              |          |   |        |        |           |
|      | Occipital |      |          |          |              |          |   |        |        |           |
|      | Lateral occipital |      |          |          |              |          |   |        |        |           |
|      | Lingual |       |          |          |              |          |   |        |        |           |
|      | Cuneus |       |          |          |              |          |   |        |        |           |
|      | Pericarinate |      |          |          |              |          |   |        |        |           |
|      |       |       |          |          |              |          |   |        |        |           |
|      | Posterior cingulate |      |          |          |              |          |   |        |        |           |
|      | Insula |       |          |          |              |          |   |        |        |           |

- **N** number of individuals in meta-analysis, *P* (Dis) two-sided p-value of discovery GWAS meta-analysis in CHARGE, *P* (Rep) two-sided p-value of replication meta-analysis in ENIGMA, *P* (Pooled) two-sided p-value of pooled discovery and replication meta-analysis. p-values are not adjusted for multiple comparisons. Banksts banks of the superior temporal sulcus.

NA, SNP or region not available in the ENIGMA sample.

In bold, significant replication (e.g. Replication < 3.1 × 10^-3) and p-values < 0.05.
| Lobe          | Region          | Locus       | Position   | Lead SNP    | Nearest gene | Annotation     | N  |
|--------------|-----------------|-------------|------------|-------------|--------------|---------------|----|
| Global       |                 | 6q22.32     | 126792095  | rs11759026  | MIR588       | Intergenic    | 22,410 |
|              |                 | 17q21.31    | 44790203   | 169201      | NSF          | Intergenic    | 22,784 |
|              |                 | 17q21.32    | 43549608   | 149366495   | PLEKHM1      | Intergenic    | 22,099 |
|              |                 | 12q14.3     | 66358347   | 1042725    | HMG2A        | 3'UTR         | 22,784 |
|              |                 | 12q23.2     | 102921296  | 11111293   | IGFI         | Intergenic    | 22,784 |
|              |                 | 6q22         | 109002042  | 49548516    | FOXO3        | 3'UTR         | 22,784 |
| Frontal      | Superior frontal| 5q14.3      | 92186429   | 8888814     | NR2F1-A51    | Intergenic    | 22,692 |
| Rostral      | Caudal anterior cingulate | 5q14 | 39636227 | 17694989 | C15orf54 | Intergenic | 22,793 |
| middle frontal |                 | 15q14       | 39636227   | 17694989    | C15orf54     | Intergenic    | 22,793 |
| Caudal       | Caudal middle frontal | 2q12.1 | 105460333  | 745249     | LINCO1158    | ncRNA_intronic | 22,726 |
|              |                  | 6q22.32     | 127068983  | 853974      | RSP03        | Intergenic    | 22,351 |
| Paras         | Paras opercularis | 5q23.3    | 128734008  | 12187568    | ADAMTS19     | Intergenic    | 20,753 |
|              | Paras triangularis | 3q24     | 147106319  | 2279829    | ZIC4         | UTR3          | 22,759 |
|              | Lateral orbitofrontal | 14q22.2   | 54769839   | 65572946    | CDKN3        | Intergenic    | 22,801 |
| Precentral   | Precentral      | 15q14       | 39634222   | 1080066     | C15orf54     | Intergenic    | 22,699 |
| Temporal     | Superior temporal | 10q25.3    | 118648841  | 3781566    | SHTN1        | Intergenic    | 22,699 |
|              | Inferior parietal | 20q13.2    | 5248936   | 6097618     | SUMO1P1      | Intergenic    | 22,701 |
|              | Supramarginal    | 12q14.3     | 65797096   | 2336713     | MSRB3        | Intergenic    | 22,701 |
|              | Supramarginal    | 3q13.11     | 104724634  | 971551      | ALCAM        | Intergenic    | 22,701 |
|              | Supramarginal    | 14q22.1     | 59627631   | 71471500    | THBS1        | Intergenic    | 22,645 |
|              | Postcentral      | 15q14       | 39633904   | 2033939     | C15orf54     | Intergenic    | 22,723 |
|              | Postcentral      | 16q24.2     | 87225319   | 4843227    | LOC101928708 | Intergenic    | 22,723 |
|              | Postcentral      | 19p13.2     | 13109763   | 68175985    | NFIX         | Intergenic    | 21,777 |
|              | Precuneus        | 1q23.1      | 59628609   | 74826997    | DAAM1        | Intergenic    | 22,803 |
|              | Precuneus        | 3q28        | 19066355   | 35055419    | OSTN         | Intergenic    | 22,428 |
|              | Occipital        | 2p22.2      | 37818236   | 2215055    | CDC4EP3      | Intergenic    | 22,803 |
|              | Occipital        | 3q13.11     | 104713881  | 12495603    | ALCAM        | Intergenic    | 22,803 |
|              | Pericalcarine    | 14q22.1     | 59625997   | 73313052    | DAAM1        | Intergenic    | 22,805 |
|              | Pericalcarine    | 11p13.5     | 12072213   | 1102231     | DKK3         | Intergenic    | 22,799 |
|              | Pericalcarine    | 13q31.1     | 80192236   | 9545156     | LINCO1068    | Intergenic    | 22,799 |
|              | Caudal anterior cingulate | 1q4.3     | 82852578   | 309588      | VCAN         | Intergenic    | 22,748 |
|              | Caudal anterior cingulate | 11q23.1    | 110949402  | 3321403     | C15orf53     | Intergenic    | 22,543 |
|              | Caudal anterior cingulate | 8q24.12    | 120596023  | 10283100    | ENPP2        | Exonic        | 21,481 |

Table 3 Genome-wide significant associations (\(p_{\text{Discovery}} < 1.0 \times 10^{-9}\) of global and regional CV.}
Supplementary Data 22 and 23. For global CTh, we found enrichment for super-enhancers, introns and histone marks. Repressors and histone marks were enriched for global CSA, and introns, super-enhancers, and repressors for global CV. For regional CSA and CV the highest enrichment scores (>18) were observed for conserved regions.

**Genetic correlation.** We found high genetic correlation ($r_g$) between global CSA, and global CV ($r_g = 0.81, P_{LDSSR} = 1.2 \times 10^{-186}$) and between global CTh and global CV ($r_g = 0.46, P_{LDSSR} = 1.4 \times 10^{-14}$), but not between global CTh and global CSA ($r_g = -0.02, P_{LDSSR} = 0.82$). Whereas the genetic correlation between CSA and CV was strong ($r_g > 0.7$) in most of the regions (Supplementary Data 24 and Supplementary Fig. 12), it was generally weak between CSA and CTh with $r_g < 0.3$, and ranged from 0.09 to 0.69 between CTh and CV. The postcentral and lingual cortices were the two regions with the highest genetic correlations between both CTh and CV, as well as CTh and CSA.

Genetic correlation across the various brain regions for CTh (Supplementary Fig. 13, Supplementary Data 25), CSA (Supplementary Fig. 14, Supplementary Data 26), and CV (Supplementary Fig. 15, Supplementary Data 27) showed a greater number of correlated regions for CTh and greater inter-regional variation for CSA and CV. Supplementary Data 28–30 and Supplementary Figs. 16–18 show genome-wide genetic correlations between the cortical measures and anthropometric, neurological and psychiatric, and cerebral structural traits.

**Discussion**

In our genome-wide association study of up to 22,824 individuals for MRI determined cortical measures of global and regional thickness, surface area, and volume, we identified 160 genome-wide significant associations across 19 chromosomes. Heritability was generally higher for cortical surface area and volume than for thickness, suggesting a greater susceptibility of cortical thickness to environmental influences. We observed strong genetic correlations between surface area and volume, but weak genetic correlation between surface area and thickness. We identified the largest number of novel genetic associations with cortical volumes, perhaps due to our larger sample size for this phenotype, which was assessed in all 21 discovery samples.
It is beyond the scope of our study to discuss each of the 160 associations identified. A large number of the corresponding genes are involved in pathways that regulate morphogenesis of neurons, neuronal cell differentiation, and cell growth, as well as cell migration and organogenesis during embryonic development. At a molecular level, the wnt/β-catenin, TGF-β, and sonic hedgehog pathways are strongly implicated. Gene-set-enrichment analyses revealed biological processes related to brain morphology and neuronal development.

Broad patterns emerged showing that genes determining cortical structure are also often implicated in development of the cerebellum and brainstem (KIAA0586, ZIC4, ENPP2) as well as the neural tube (one carbon metabolism genes DHFR and MSRBB3, the latter also associated with hippocampal volumes25). These genes determine development of not only neurons but also astroglia (THBS1) and microglia (SALL1). They determine susceptibility or resistance to a range of insults: inflammatory, vascular (THBS1, ANXA1, ARRDC3-AS1)26) and neurodegenerative (C15orf53, ZIC4, ANXA1), and have been associated with pediatric and adult psychiatric conditions (THBS1).

There is a wealth of information in the supplementary tables that can be mined for a better understanding of brain development, connectivity, function and pathology. We highlight this potential by discussing in additional detail, the possible
immune-inflammatory conditions. Nitric oxide signaling, which plays a role in several cancers and astrocyte induced synaptogenesis, and regulates chain migration stream to the olfactory bulb. Moreover, thickness, surface area, and volume of the middle temporal regions at low 6q22.32, 17q21.31, and 3q24, associate with multiple brain regions across six other regions in the frontal and parietal lobes. Lead SNPs at this locus were either intergenic between C15orf53 and C15orf54, or intergenic between C15orf54 and THBS1 (Thrombospondin-1). C15orf53 has been associated with an autosomal recessive form of spastic paraplegia showing intellectual disability and thinning of the corpus callosum (hereditary spastic paraparesis 11, or Nakamura Osame syndrome). Variants of THBS1 were reported to be related to autism and schizophrenia. The protein product of THBS1 is involved in astrocyte induced synaptogenesis, and regulates chain migration of interneuron precursors migrating in the postnatal radial migration stream to the olfactory bulb. Moreover, THBS1 is an activator of TGFβ signaling, and an inhibitor of pro-angiogenic nitric oxide signaling, which plays a role in several cancers and immune-inflammatory conditions.

Variants at Chr14q23.1 were associated with cortical surface area and volume of all regions in the occipital lobe, as well as with thickness, surface area, and volume of the middle temporal cortex, banks of the superior temporal sulcus, fusiform, supramarginal and precuneus regions, areas associated with discrimination and recognition of language or visual form. These variants are either intergenic between KIAA0586, the product of which is a conserved centrosomal protein essential for ciliogenesis, sonic hedgehog signaling and intracellular organization, and DACT1, the product of which is a target for SIRT1 and acts on the wnt/β-catenin pathway. KIAA0586 has been associated with Joubert syndrome, another condition associated with abnormal cerebellar development. Other variants are intergenic between DACT1 and DAAM1 or intergenic in DAAM1. DAAM1 has been associated with occipital lobe volume in a previous GWAS. Locus 6q22.32 contains various SNPs associated with cortical surface area and volume globally, and also within some frontal, temporal and occipital regions. The SNPs are intergenic between RSPO3 and CENPW. RSPO3 and CENPW have been previously associated with intracranial32,33 and occipital lobe volumes. RSPO3 is an activator of the canonical Wnt signaling pathway and a regulator of angiogenesis.

Chr17q21.31 variants were associated with global cortical surface area and volume and with regions in temporal lobe. These variants are intronic in the genes PLEKHM1, CRHR1, NSF, and WNT3. In previous GWAS analyses, these genes have been associated with general cognitive function and neuroticism. Variants at Chr17q21.31 were associated with cortical surface area and volume globally, and also within some frontal, temporal and occipital regions. The SNPs are intergenic between RSPO3 and CENPW. RSPO3 and CENPW have been previously associated with intracranial32,33 and occipital lobe volumes. RSPO3 is an activator of the canonical Wnt signaling pathway and a regulator of angiogenesis.

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The protein product of the gene ZIC4 is a C2H2 zinc finger transcription factor that has an intraneuronal, non-synaptic expression and auto-antibodies to this protein have been associated with subacute sensory neuronopathy, limbic encephalitis, and seizures in patients with breast, small cell lung or ovarian cancers. ZIC4 null mice have abnormal development of the visual pathway and heterozygous deletion of the gene has also been associated with a congenital cerebellar (Dandy-Walker) malformation, thus implicating it widely in brain development as well as in neurodegeneration. C2H2ZF transcription factors are the most widely expressed transcription factors in eukaryotes and show associations with responses to abiotic (environmental) stressors. Another transcription factor, FOXC1, also associated with Dandy-Walker syndrome has been previously shown to be associated with risk of all types of ischemic stroke and with stroke

**Fig. 3** Functional annotation categories for global and regional CTh, CSA, and CV. Proportion of functional annotation categories for global and regional cortical thickness (blue), surface area (light green), and volume (yellow) assigned by ANNOVAR.

**Fig. 4** Number of overlapping genes between gene mapping methods. Number of overlapping genes between FUMA eQTL mapping, FUMA chromatin interaction mapping, ANNOVAR chromosome positional mapping, and MAGMA gene-based analysis for all cortical regions combined for cortical surface area (a), thickness (b) and volume (c).
severity. Thus, ZIC4 might be a biological target worth pursuing to ameliorate neurodegenerative disorders.

We found an exonic SNP within the gene ENPP2 (Autotaxin) at 8q24.12 to be associated with insular cortical volume. This gene is differentially expressed in the frontal cortex of Alzheimer patients and in mouse models of Alzheimer disease, such as the senescence-accelerated mouse prone 8 strain (SAMP8) mouse. Autotaxin is a dual-function ectoenzyme, which is the primary source of the signaling lipid, lysophosphatidic acid. Besides Alzheimer disease, changes in autotaxin/lysophosphatic acid signaling have also been shown in diverse brain-related conditions, such as intractable pain, pruritus, glioblastoma, multiple sclerosis, and schizophrenia. In the SAMP8 mouse, improvements in cognition noted after administration of LW-AFC, a putative Alzheimer remedy derived from the traditional Chinese medicinal prescription ‘Liwei Dihuang’ decoction, are correlated with restored expression of four genes in the hippocampus, one of which is ENPP2.

Among the other genetic regions identified, many have been linked to neurological and psychiatric disorders, cognitive functioning, cortical development, and cerebral structure (detailed listing in Supplementary Data 31).

Heredity estimates are, as expected, generally higher in the family-based Austrian Stroke Prevention-Family study (ASPS-Fam) than in the Rotterdam Study (RS) for CTh (average $h^2_{ASPS-Fam} = 0.52$; $h^2_{RS} = 0.26$), CSA (0.62 and 0.30) and CV (0.57 and 0.23). This discrepancy is explained by the different heritability estimation methods: pedigree-based heritability in ASPS-Fam versus heritability based on common SNPs that are in LD with causal variants in RS.

Average heritability over regions is also higher for surface area and volume, than for thickness. The observed greater heritability of CSA compared to CTh is consistent with the previously articulated hypothesis, albeit based on much smaller numbers, that CSA is developmentally determined to a greater extent with smaller subsequent decline after young adulthood, whereas CTh changes over the lifespan as aging, neurodegeneration and vascular injuries accrue. It is also interesting that brain regions more susceptible to early amyloid deposition (e.g., superior temporal cortex and precuneus) have a higher heritability.

We found no or weak genetic correlation between CTh and CSA, globally and regionally, and no common lead SNPs, which indicates that these two morphological measures are genetically independent, a finding consistent with prior reports. In contrast, we found strong genetic correlation between CSA and CV and identified common lead SNPs for CSA and CV globally, and in 12 cortical regions. Similar findings have been reported in a previous publication. The genetic correlation between CTh and CV ranged between 0.09 and 0.77, implying a common genetic background in some regions (such as the primary sensory postcentral and lingual cortices), but not in others. For CTh, we observed genetic correlations between multiple regions within each of the lobes, whereas for CSA and CV, we found genetic correlations mainly between different regions of the occipital lobe. Chen et al. have also reported strong genetic correlation for CSA within the occipital lobe. There were also a few genetic correlations observed for regions from different lobes, suggesting similarities in cortical development transcended traditional lobar boundaries.

A limitation of our study is the heterogeneity of the MR phenotypes between cohorts due to different scanners, field strengths, MR protocols and MRI analysis software. This heterogeneity as well as the different age ranges in the participating cohorts may have caused different effects over the cohorts. We nevertheless combined the data of the individual cohorts to maximize the sample size as it has been done in previous CHARGE GWAS analyses. To account for the heterogeneity we used a sample-size weighted meta-analysis that does not provide overall effect estimates. This method has lower power to detect associations compared to inverse-variance weighted meta-analysis and we therefore may have found less associations.

Methods

Study population. The sample of this study consists of up to 22,824 participants from 20 population-based cohort studies collaborating in the Cohorts of Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium and the UK Biobank (UKBB). All the individuals were stroke- and dementia free, aged between 20 and 100 years, and of European ancestry, except for ARIC AA with African ancestry. Supplementary Data 32 provides population characteristics of each cohort and Supplementary Methods provide a short description of each cohort. Each study secured approval from institutional review boards or equivalent organizations, and all participants provided written informed consent. Our results were replicated using summary GWAS findings of 22,635 individuals from the ENIGMA consortium.

Genotyping and imputation. Genotyping was conducted using various commercially available genotyping arrays across the study cohorts. Prior to imputation, extensive quality control was performed in each cohort. Genotype data were imputed to the 1000 Genomes reference panel (mainly phase 1, version 3) using validated software. Details on genotyping, quality control and imputation can be found in Supplementary Data 33.

Phenotype definition. This study investigated CTh, CSA, and CV globally in the whole cortex and in 34 cortical regions. Global and regional CTh was defined as the mean thickness of the left and the right hemisphere in millimeter (mm). Global CSA was defined as the total surface area of the left and the right hemisphere in mm², while regional CSA was defined as the mean surface area of the left and the right hemisphere in mm². Global and regional CV was defined as the mean volume of the left and the right hemisphere in mm³. The 34 cortical regions are listed in the Supplementary Methods. High resolution brain magnetic resonance imaging (MRI) data was obtained in each cohort using a range of MRI scanners, field strengths and protocols. CTh, CSA, and CV were generated using the Freesurfer software package in all cohorts except for FHScar, where an in-house segmentation method was used. MRI protocols of each cohort can be found in Supplementary Data 35 and descriptive statistics of CTh, CSA, and CV can be found in Supplementary Data 36–38.

Genome-wide association analysis. Based on a predefined analysis plan, each study fitted linear regression models to determine the association between global and regional CTh, CSA, and CV and allele dosages of SNPs. Additive genetic effects were assumed and the models were adjusted for sex, age, age², and if needed for study site and for principal components to correct for population stratification. Cohorts including related individuals calculated linear mixed models to account for family structure. Details on association software and covariates for each cohort are shown in Supplementary Data 33. Models investigating regional CTh, CSA, and CV were additionally adjusted for global CTh, global CSA and global CV, respectively. Quality control of the summary statistics shared by each cohort was performed using EasyQC. Genetic variants with a minor allele frequency (MAF) <0.05, low imputation quality ($R^2 < 0.4$), and which were available in less than 10,000 individuals were removed from the analyses. Details on quality control are provided in the Supplementary Methods.

We then used METAL to perform meta-analyses using the z-scores method, based on p-values, sample size, and direction of effect, with genomic control correction. To estimate the number of independent tests for the p-value threshold correction, we used a non-parametric permutation testing procedure in the
combined Rotterdam Study cohort (N = 4442) and UK Biobank (N = 8213). First, we generated a random independent variable, to insure that there is no true relationship between the measurements and this variable. Second, we ran linear regression analyses between this variable and all brain measurements one-by-one in each of the cohorts separately (104 regressions in total per cohort). Third, we saved the minimum p-value obtained from those 104 regressions. Then, as suggested in literature, we repeated this procedure 10,000 times. Therefore, at the end we have 10,000 minimum p-values per cohort. The minimum p-value distribution follows a Beta distribution Beta(m,n), where m = 1 and n is the degree of freedom, which represents the number of independent tests in case of permutation testing. Using python statistical library we fitted the Beta function with the minimum p-values, and found m for Rotterdam Study and UK Biobank identically equal to 46. Based on the permutation test results, the genome-wide significance threshold was set a priori at 1.99 × 10^{-15} (5 × 10^{-9/46}). We used the clumping function in PLINK (linkage disequilibrium (LD) threshold: 0.2, distance: 300 kb) to identify the most significant SNP in each LD block. We used LDRS to calculate genomic inflation factors (λEC), LDRS intercepts and LDRS ratios for each meta-analysis. The LDRS intercept was estimated to differentiate between inflation due to a polygenic signal and inflation due to population stratification. The LDR ratio represents the amount of inflation that is due to other causes than polygenicity such as population stratification or cryptic relatedness.

For replication of our genome-wide significant CTs and CSA associations, we used GWAS meta-analysis results from the ENIGMA consortium for all SNPs that were associated at a p-value <5 × 10^{-8} and performed a pooled meta-analysis. The p-value threshold for replication was set to 3.1 × 10^{-4} (0.05/160: nominal significance threshold divided by total number of lead SNPs). CV was not available in the ENIGMA results, PRS analysis was performed for 7800 out of sample subjects (not included in the current GWAS) from UK Biobank cohort using the PSiSeq-2 software with standard settings. The significance threshold for the association between the PRS and the phenotype was set to 4.76 × 10^{-3} (0.05/105: nominal significance threshold divided by number of CVAS phenotypes). The NHGRI-EBI Catalog of Single-Nucleotide Variants (dbSNP) was searched for the significant SNP-trait associations at a p-value of 5 × 10^{-8} of lead SNPs. Regional association plots were generated with LocusZoom, and the chromosomal ideogram with PHENOGRAM (http:// visualization.ritchielab.org/phenogram/plots).

Annotation of genome-wide significant variants was performed using the ANNOVAR software package and the FUMA web application. FUMA eQTL mapping uses information from three data repositories (GTEx, Blood eQTL browser, and BIOS QTTL browser) and maps SNPs to genes based on a significant eQTL association. We used a false discovery rate threshold (FDR) of 0.05 divided by number of tests (46) to define significant eQTL associations. Gene-based analyses, to combine the effects of SNPs assigned to a gene, and gene set analyses, to find out if genes assigned to significant SNPs were involved in biological pathways, were performed using MAGMA as implemented in FUMA. The significance threshold set to 5.87 × 10^{-8} (0.05/1852274: FDR threshold divided by number of genes and independent tests) for gene-based analyses and to 1.02 × 10^{-7} (0.05/10651: FDR threshold divided by the number of gene sets) for the gene set analyses. Additionally, FUMA was used to investigate a significant chromatin interaction between a genomic region in a risk locus and promoter regions of genes (250 bp upstream and 500 bp downstream of a TSS). We used an FDR of 1 × 10^{-4} to define significant interactions.

We investigated cis (≤1 MB) and trans (>1 MB or on a different chromosome) expression quantitative trait loci (eQTL) for genome-wide significant SNPs in 724 post-mortem brains from ROSMAP stored in the AMP-AD database. The significance threshold was set to 0.001 (0.05/46: FDR threshold divided by the number of independent tests). For additional pathway analyses of genes that were mapped to independent lead SNPs by FUMA, we searched the InnateDB database. The STRING database was used for visualizing protein–protein interactions. Only those protein subnetworks with five or more nodes are shown.

Heritability. Additive genetic heritability (h^2) of CTs, CSA, and CV was estimated in two studies: the Australian Stroke Prevention Family Study (ASPF-Fam; n = 365) and the Rotterdam Study (RS, n = 4472). In the population-based family study ASPF-Fam, the ratio of the genotypic variance to the phenotypic variance was calculated using variance components models in SOLAR. In case of non-normal phenotype data were inverse-normal transformed. In RS, SNP-based heritability was computed with GCTA. These heritability analyses were adjusted for age and sex.

Heritability and partitioned heritability based on GWAS summary statistics was calculated from GWAS summary statistics using LDRS implemented in the LDSC tool. Partitioned heritability analysis splits genome-wide SNP heritability into 53 functional annotation classes (e.g., coding, 3’UTR, promoter, transcription factor binding sites, conserved regions etc.) and additionally to 10 cell-type specific classes (e.g., central nervous system, cardiovascular, liver, skeletal muscle, etc.) as defined by Finucane et al. to evaluate the contribution to heritability. The signif. independent level was set to 2.05 × 10^{-6} (0.05/53*10^6: nominal significance divided by number of functional annotation classes and number of independent tests) for heritability partitioned on annotation classes and cell types.

Genetic correlation. LDRS genetic correlation between CTs, CSA, and CV was estimated globally and within each cortical region. The significance threshold was set to 7.35 × 10^{-4} (nominal threshold (0.05) divided by number of regions (34) and by number of correlations (CSA and CV, CSA and CTs). Genetic correlation was also estimated between all 34 cortical regions for CTs, CSA, and CV, with the significance threshold set to 8.91 × 10^{-5} (nominal threshold (0.05) divided by number of regions (34) times the number of regions −1 (33) divided by 2 (half of the matrix)). Additionally, the amount of genetic correlation was quantified between CTs, CSA, and physical traits (height, body mass index), neurological and psychiatric diseases (e.g., Alzheimer’s disease, Parkinson’s disease), cognitive traits and MRI volumes (p-value threshold (0.05/64/number of GWAS traits). As recommended by the LDSC tool developers, only HapMap3 variants were included in these analyses, as these tend to be well-imputed across cohorts.

Reporting summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

The genome-wide summary statistics that support the findings of this study are available via the CHARGE Summary Results portal at the NCBi dbGaP website https://www. omicstudio.com/dataset/dbgap/phs000930 upon publication, or from the corresponding authors R.S. and S.S. upon reasonable request. The summary statistics may be used for all scientific purposes except for the study of potentially sensitive and potentially stigmatizing phenotypes such as intelligence and addiction, since this is proscribed by the consent terms for the NHSLBI cohorts. Individual level data or study-specific summary results are only available through controlled access. Data for the Framingham Study are available through dbGaP, where qualified researchers can apply for authorization to access (https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000607. v30.p1). Individual level data for the ARIC and CHS studies are also available through dbGaP. Data of European and Australian cohorts are available upon request, in keeping with data sharing guidelines in the EU General Data Protection Regulation. Data from UK Biobank can be accessed at http://www.ukbiobank.ac.uk and for the ENIGMA consortium from medlandse@gmail.com. Individual level data for VETAS is not available due to consent restrictions.

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Author contributions
Dr. Dale is a founder of and holds equity in CorTechs Labs, Inc, and serves on its Scientific Advisory Board. He is a member of the Scientific Advisory Board. W. Niessen is a founder and shareholder of Quantib BV. H. Brodaty is an advisory board member of Nutricia. The other authors declare no competing interests.

Competing interests

Additional information

Supplementary information

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