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Genetic variants associated with longitudinal changes in brain structure across the lifespan

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Abstract

Human brain structure changes throughout our lives. Altered brain growth or rates of decline are implicated in a vast range of psychiatric, developmental, and neurodegenerative diseases. Here, we identified common genetic variants that affect rates of brain growth or atrophy, in the first genome-wide association meta-analysis of changes in brain morphology across the lifespan. Longitudinal MRI data from 15,640 individuals were used to compute rates of change for 15 brain structures. The most robustly identified genes *GPR139*, *DACHI* and *APOE* are associated with metabolic processes. We demonstrate global genetic overlap with depression, schizophrenia, cognitive functioning, insomnia, height, body mass index and smoking. Gene-set findings implicate both early brain development and neurodegenerative processes in the rates of brain changes. Identifying variants involved in structural brain changes may help to determine biological pathways underlying optimal and dysfunctional brain development and ageing.

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Code availability:

The code for processing of individual cohorts (including imaging and QC, imputation and GWAS protocol) can be found on <http://enigma.ini.usc.edu/ongoing/enigma-plasticity-working-group/>. Code for the meta-regression is available through Github https://github.com/RMBrouwer/GWAS_meta_regression.

Competing interests:

Other authors declare no conflict of interest.

Under the influence of genes and a varying environment, human brain structure changes throughout the lifespan. Even in adulthood, when the brain seems relatively stable, individuals differ in the profile and rate of brain changes¹. Longitudinal studies are crucial to identify genetic and environmental factors that influence the rate of these brain changes throughout development² and ageing³. Inter-individual differences in brain development are associated with general cognitive function^{4,5}, and risk for psychiatric disorders^{6,7} and neurological diseases^{8,9}. Genetic factors involved in brain development and ageing overlap with those for cognition¹⁰ and risk for neuropsychiatric disorders¹¹. A recent cross-sectional study showed brain age to be advanced in several brain disorders. Brain age is an estimate of biological age based on brain structure, which can deviate from chronological age. Several shared loci were found between the genome wide association study (GWAS) summary statistics for advanced brain age and psychiatric disorders¹². However, we still lack information on which genetic variants influence an individual's brain changes throughout life, since this requires longitudinal data. Discovering genetic factors that explain variation between individuals in brain structural changes may reveal key biological pathways that drive normal development and ageing, and may contribute to identifying disease risk and resilience: a crucial goal given the urgent need for new treatments for aberrant brain development and ageing worldwide.

As part of the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium¹³ the ENIGMA Plasticity Working Group quantified the overall genetic contribution to longitudinal brain changes, by combining evidence from multiple twin cohorts across the world¹⁴. Most global and subcortical brain measures showed genetic influences on change over time, with a higher genetic contribution in the elderly (heritability 16 – 42%). Genetic factors that influence longitudinal changes were partially independent of those that influence baseline volumes of brain structures, suggesting that there might be genetic variants that specifically affect the rate of development or ageing. However, the genes involved in these processes are still not known, with only a single, small-scale GWAS performed for longitudinal volume change in gray and white matter of the cerebrum, basal ganglia, and cerebellum¹⁵. Here, we set out to find genetic variants that may influence rates of brain changes over time, using genome-wide analysis in individuals scanned with magnetic resonance imaging (MRI) on more than one occasion. We also aimed to identify age-dependent effects of genomic variation on longitudinal brain changes in mostly healthy, but also neurological and psychiatric, populations.

In our GWAS meta-analysis, we sought genetic loci associated with annual change rates in 8 global and 7 subcortical morphological brain measures in a coordinated two-phased analysis using data from 40 longitudinal cohorts (Extended Data Fig 1 and Supplementary Table 1). We extracted global and subcortical brain measures, and assessed annual change rates, using additive genetic association analyses to estimate the effects of genetic variants on the rates of change within each cohort. As brain change is not constant over age¹ and gene expression also changes during development and ageing¹⁶, we determined whether the estimated genetic variants were age-dependent, i.e., differentially affected rates of brain changes at different stages of life, by using genome-wide meta-regression models with linear or quadratic age effects (Methods). It must be noted that although the cohorts analysed in this study together cover the full lifespan, there is relatively little age overlap between them.

This implies that we cannot rule out that cohort-specific characteristics other than age could influence our meta-regression findings.

We employed a rolling cumulative meta-analysis and -regression approach¹⁷. In phase 1, for which data collection ended on Feb 1st, 2019, we analysed the cohorts of European descent (N=9,623). We sought replication by adding data from three additional cohorts that became available after our analysis of phase 1: one developmental cohort (average age 10 at baseline) and two in ageing populations (N =5,477; all of European descent; total N=15,100 in phase 2). For all follow-up analyses we used results from phase 2. Finally, we added cohorts of non-European ancestry (total N=15,640).

Longitudinal trajectories

Brain measures showed differing trajectories of change with age (Figures 1,2 and Extended Data Video 1) - either monotonic increases (lateral ventricles), monotonic decreases (cortex volume, cerebellar grey matter volume, cortical thickness, surface area, total brain volume), or increases followed by stabilization and subsequently decreases (cerebral and cerebellar white matter, thalamus, caudate, putamen, nucleus accumbens, pallidum, hippocampus and amygdala volumes). Each brain structure showed a characteristic trajectory of change. Within two of our largest cohorts in phase 1 (one in childhood and one in older age), we computed correlations between the rates of change of all possible pairs of these 15 brain structures. These correlations in both childhood and older age were generally low in our data (Extended Data Fig. 2), except for the correlation between rates of change of cortical thickness and cortex volume. Therefore, we chose to investigate all brain structures separately, maximizing sensitivity of the GWAS to identify region-specific associations of genetic variants. Using the correlation structure, we estimated the effective number of independent variables through matrix spectral decomposition on the rates of change, yielding 14 independent traits for multiple testing corrections (Methods).

Age-independent associations

Two loci showed genome-wide significant effects on the rate of brain change in phase 1, one of which was also genome-wide significant in phase 2 (Figure 3; Supplementary Table 4; p-value replication sample 0.08). This lead SNP, rs72772740 on chromosome 16, is an intronic variant located in the *GPR139* gene and was associated with rate of change in lateral ventricle volume (Figure 4). Functional annotation identified numerous significant expression quantitative trait loci (eQTL) associations (FDR < 0.05) in different datasets and highlighted genes by either eQTL mapping (*GPRC5B*, *IQCK*, *KNOX1*, *C16orf62*) or chromatin interaction mapping (*ACSM1*, *ACSM5*, *UMOD*, *GP2*). *GPR139* is the G-protein-coupling receptor gene 139, which encodes a member of the rhodopsin family of G-protein coupled receptors. The gene is almost exclusively expressed in the central nervous system, with highest expression from 12 to 26 weeks post-conception, and has been suggested as a therapeutic target for metabolic syndromes and motor diseases¹⁸. *GPR139* may play a role in foetal brain development¹⁹. Mice lacking *GPR139* exhibited schizophrenia-like behavioural abnormalities²⁰, and functional cell assays showed the inhibitory influence of *GPR139* on dopamine receptor 2 (D2R) signalling²⁰. The second lead SNP, rs449998, an

intronic variant on chromosome 21 located in the Down Syndrome Cell Adhesion Molecule (*DSCAM*) gene, was associated with rate of change in nucleus accumbens volume in phase 1, but this association was not significant in the replication sample, or phase 2. Three SNPs were significant in the phase 2 analysis only. These include rs10990953, intergenic on chromosome 9, associated with rate of change in lateral ventricle volume; rs1425034, intergenic and located in long intergenic non-protein coding RNA on chromosome 2, associated with rate of change in pallidum volume; and rs12325429, intron of *CDH8* on chromosome 16, associated with rate of change in total brain volume (Supplementary Table 5; Supplementary Figs. 1,2 provide Manhattan plots, QQ plots, locus plots and circos plots). The association of *CDH8* with total brain volume rate of change is particularly interesting, since *CDH8* has been associated previously with learning disability and autism²¹. *CDH8* is a protein-coding gene and encodes a type II classical cadherin from the cadherin superfamily, integral membrane proteins that mediate calcium-dependent cell–cell adhesion. Genome-wide significant SNPs in phase 1 or phase 2 did not show heterogeneity ($I^2 < 10.2$; $p(I^2) > 0.31$; Supplementary Tables 4,5, Supplementary Fig.3 for forest plots).

Age-dependent associations

Three additional loci had an association with rate of change that was variable across the lifespan in phase 1 (Figure 3; Supplementary Tables 6,8). For two of these, the association remained significant in the phase 2 analysis: rate of change in white matter cerebrum volume was affected by rs573983368 (intronic variant) in the Dachshund Family Transcription Factor 1 (*DACHI*) gene, and 5:157751672 (intergenic and located in long intergenic non-protein coding RNA LINC02227) on chromosome 5 had an age-dependent effect on the rate of change in surface area (Figure 4; Supplementary Tables 6-9). Rate of change in cerebellar white matter volume was affected by the intronic rs10674957 in the Thyrotropin Releasing Hormone Degrading Enzyme (*TRHDE*) gene, but this third locus was not significant in phase 2.

The *DACHI* locus shows significant chromatin interaction, which can play an important role in gene expression regulation. *DACHI* encodes a chromatin-associated protein that associates with DNA-binding transcription factors to regulate gene expression and cell fate determination during development. *DACHI* is highly expressed in the proliferating neural progenitor cells of the developing cortical ventricular and subventricular regions, and in the striatum²². We found the effect of *DACHI* to have a quadratic age-dependence, with the variant being associated with faster growth in childhood and earlier but slower decline with ageing (Figure 4). The effect of 5:157751672 had a linear age-dependence, with the tested variant being associated with less growth of surface area in childhood, and less decline at older age.

For seven additional loci we found a significant age-dependent association with rate of change only in phase 2 (Supplementary Tables 7,9; Supplementary Figs. 1,2 provide Manhattan plots, QQ plots, locus plots and circos plots). One of these, rs429358, a missense variant of the Alzheimer's disease (AD)-related²³ apolipoprotein E gene (*APOE*) gene, was associated with change rate in hippocampus, showing prolonged growth into adulthood and faster reductions of volume of the hippocampus for carriers of the AD risk variant. *APOE*

plays a role in maintenance of cellular cholesterol homeostasis by delivering cholesterol to neurons on apoE-containing lipoprotein particles. Cholesterol is important for synapse and dendrite formation, and cholesterol depletion has been shown to cause synaptic and dendritic degeneration²⁴. Other findings include rs12019523, an intronic variant in the *CAB39L* gene associated with rate of change of the caudate volume; rs34342646, an intronic variant in the *NECTIN2* gene associated with rate of change in surface area and rs73210410, an intronic variant in the *SORCS2* gene associated with rate of change in pallidum volume.

To visualize the age-dependent effects, we plotted the meta-regression results for the significant loci (Methods, Supplementary Fig. 3). Genome-wide significant SNPs in phase 1 or phase 2 did not show significant residual heterogeneity ($p > 0.23$; except for the age-dependent effect of rs429358 on hippocampus change rate ($p=0.02$)). A summary of the genome-wide significant results and the top-10 loci for each phenotype and age model are presented in Supplementary Tables 4-9.

Gene-based analyses

Gene-based associations with all phenotypes were estimated using MAGMA (Methods). We found six genome-wide significant genes influencing structural rates of change in phase 1, four of which were also significant in phase 2 (Supplementary Table 10, 11); among these, *DACHI* and *GPR139*, which were implicated through SNP-based GWAS, also reached genome-wide significance in this gene-based GWAS. In addition, we found *APOE* to be associated with change rates for both hippocampus and amygdala. The phase 2 analysis showed two new findings: an association of the *FAU* gene with rate of change in cerebellum white matter volume, and again *APOE*, associated with rate of change in surface area. Of note, the *APOE* findings were based on GWAS and subsequent gene analysis, and we did not investigate the classical *APOE* status, since that is determined by a combination of two SNPs. However, we observed that the effect of *APOE* on change rate of hippocampus and amygdala was fully driven by rs429358, with the risk variant for AD causing prolonged growth into adulthood and faster decay for both amygdala and hippocampus volumes later in life.

To visualize the age-dependent effects, we plotted the meta-regression results for the top SNP in each of the significant genes (Supplementary Fig. 3). Supplementary Tables 10, 11 display the top-10 genes for each phenotype and each age model. Supplementary Table 12 details putative biological functions of associated genes and genes harbouring genome-wide significant associated loci.

Gene-set analyses

To test whether genetic findings for brain structure change converged onto functional gene sets and pathways, we conducted gene-set analyses using MAGMA (Methods). Competitive testing was used and 10 and 12 genome-wide significant gene sets were found for phase 1 and phase 2, respectively (Supplementary Tables 13, 14 for top-10 gene sets and genes included). Two main themes emerge from this analysis, as biological functions of

the gene sets converge onto involvement in early brain development and involvement in neurodegeneration, respectively.

One gene set was significant in both the phase 1 and phase 2 analyses, i.e. GO_neural_nucleus_development. This gene set consists of genes involved in the development of neural nuclei (compact clusters of neurons in the brain) and was associated with rates of change in cerebellar white matter volume in our study. Two other gene sets, significant in phase 1 (GO_substantia_nigra_development associated with rate of change in cerebellum white matter volume) and phase 2 (GO_midbrain_development associated with quadratic age-dependent surface area rates of change) were closely related to neural nucleus development in gene ontology terms.

The most significant gene set was GO_response_to_phorbol_13_acetate_12_myristate (p -value=1.42e-08) in phase 2, related to surface area change. Phorbol 13-acetate 12-myristate is a phorbol ester and an activator of protein kinase C (PKC)²⁵. Two other gene sets, significant in phase 2 (GO_tau_protein_binding and GO_tau_protein_kinase_activity) and both associated with rate of change in caudate volume, imply genes involved in interacting with tau protein. Tau is a microtubule-associated protein, implicated in Alzheimer's disease, Down Syndrome and amyotrophic lateral sclerosis (ALS).

Follow-up analyses: overlap with cross-sectional findings

SNP-based heritability estimates (h^2) of the rates of change based on linkage disequilibrium score regression (LDSC; Methods) were small overall (Supplementary Table 15). For all phenotypes, the h^2 z-score was below 4. We thus tested for genetic overlap with cross-sectional brain data and other phenotypes by applying approaches other than LDSC, although these do not provide a measure of genetic correlation. To investigate whether cross-sectional GWAS for brain structure and our GWAS on rates of change identify the same or different genetic variants, we investigated overlap between rate of change and earlier published data on cross-sectional brain structure of the same structure, where available (Methods). Supplementary Fig. 4 displays the number of overlapping genes tested against the expected number of overlapping genes that would occur by chance, in the first 1–1,000 ranked genes. Supplementary Table S11 lists the top-10 gene findings for each of the 15 change-rate phenotypes and compares these with the gene ranks from cross-sectional data. In the top-10 ranked genes, *APOE* for hippocampus occurred in the top-10 for both cross-sectional data²⁶ and age-dependent effects on rate of change ($p=0.006$). No overlap was seen for the other measured phenotypes. Extending this search to the top 200 (~1% of genes), we found overlapping genes above chance level for cortical thickness of quadratic age-dependent genes and cross-sectional findings ($p = 8.39e-05$). In the top 1,000 ranked genes (~5% of genes), further overlapping genes did emerge (Supplementary Fig. 4). Overlapping genes at such a high aggregate level imply that largely different genetic backgrounds underlie changes in brain structure and brain structure per se.

To test for global genomic overlap between our findings and GWAS of cross-sectional volumes we applied independent SNP-Effect Concordance Analyses (iSECA) (Methods) and tested for pleiotropy. We found no significant pleiotropy between longitudinal and

cross-sectional results, confirming a largely different genetic background for changes in brain structure and brain structure *per se* (Figure 5).

Follow-up analyses: overlap with other traits

We applied iSECA for overlap between our age-independent summary statistics for structural brain changes and several neuropsychiatric, neurological, physical, ageing and disease-related phenotypes and psychological traits (Methods). We found significant genomic overlap ($p < 1.6e-04$) with genetic variants associated with depression²⁷, schizophrenia²⁸, cognitive functioning²⁹, height³⁰, insomnia³¹, body mass index (BMI)³⁰ and ever-smoking³². Despite significant pleiotropy between rates of change and these traits, we did not find evidence for concordance or discordance of effects (Figure 5, Supplementary Figure 5). For comparison, we computed the genomic overlap between cross-sectional volumes and these phenotypes using the same method. In general, cross-sectional volumes showed overlap for the same traits and several others. Of note, there was also little overlap between the summary statistics for the longitudinal brain measures and summary statistics for the corresponding volumes, based on cross-sectional data. This implies that despite the fact that both cross-sectional brain volume and rates of changes are associated with traits such as schizophrenia or cognitive functioning, these associations are likely not driven by the same genomic locations. Additionally, there was little overlap in the genetic loci associated with the longitudinal brain measures and intracranial volume at baseline, indicating that overall head size did not drive our findings (Figure 5).

Follow-up analyses: gene expression across the lifespan

We determined mRNA expression for genome-wide significant genes and genes associated with genome-wide significant SNPs (Supplementary Tables S5,7,9) in 54 tissue types and in both the developing and adult human brain (Methods). For the prioritized genes, a gene expression heatmap was created, based on GTEx v8 RNAseq data³³. This revealed considerable expression levels across several brain tissues for the following genes: *APOE*, *CAB39L*, *FAU*, *NECTIN2* (alias *PVRL2*) and *SORCS2*, the latter showing higher expression in brain tissue compared to all other tissue types (Supplementary Fig. 6A). These genes show different expression patterns across the lifespan in the BrainSpan data³⁴. *DACHI* shows highest expression during early prenatal stages (8–9 post conception weeks), compared to postnatal stages. Several genes demonstrate stable high expression levels throughout development and across the lifespan (*APOE*, *CAB39L*, *FAU*, *NECTIN2* (alias *PVRL2*)). *CDH8* shows lower expression in the early prenatal stages and higher expression later in life (Supplementary Fig. 6B).

Follow-up analyses: phenome-wide associations

For the prioritized SNPs and genes (Supplementary Tables 5,7,9,11), exploratory pheWAS (i.e., ‘phenome-wide’) analysis was performed to systematically analyse many phenotypes for association with the genotype and individual genes (Supplementary Table 17). PheWAS was performed using publicly available data from the GWASAtlas³² (<https://atlas.ctglab.nl>). Gene associations of *DACHI*, *GPR139* and *SORCS2* showed pleiotropic

effects mainly in the metabolic domain, e.g., with estimated glomerular filtration rate and BMI (Supplementary Table 17, Supplementary Fig. 7). *SORCS2* and *CDH8* also showed significant associations with psychiatric and cognitive traits. Both *APOE* and *NECTIN2* showed strongest associations with Alzheimer's disease, cholesterol and lipids (Supplementary Table 17, Supplementary Fig. 7).

Sensitivity analyses

We repeated the SNP and gene analyses in various subgroups: 1) by adding four cohorts of non-European or mixed ancestry (N=540; total N=15,640); 2) by omitting cohorts that did not meet a minimum sample size criterion (N>75) or a minimum scanning interval (> 0.5 years) leaving N=14,601; 3) by excluding diagnostic groups in each cohort, leaving N=13,034, and 4) by including a covariate adjusting for disease status (Supplementary Tables 18,19). In SNP-based and gene-based analyses, effect sizes of SNPs were very similar in all subgroups, suggesting that our results are also applicable for individuals of non-European ancestry (with the caveat that the non-European subgroup was rather small) and were not driven by the smaller cohorts. Findings were also similar in the healthy subgroup and when correcting for disease status, with one notable exception: the association between *APOE* and rate of volume change in hippocampus and amygdala, with increasing influence of the top SNP with age, was no longer present after correcting for disease (see Supplementary Table 1 for diagnoses). This suggests that these *APOE* findings were in part driven by the presence of patients in the cohorts and could therefore be explained either by disease-related genes that also influence rates of change or by brain changes occurring as a consequence of the disease.

Given that our main analyses included patients, and iSECA analyses showed several associations with disease, we repeated iSECA analyses excluding diagnostic groups in each cohort. These analyses implicate the same traits, associated with largely the same rates of change of brain measures (Supplementary Fig. 5).

Discussion

Here, we present the first GWAS investigating influences of common genetic variants on brain-structural changes in over 15,000 subjects covering the lifespan. The longitudinal design of our study combined with the large age range assessed provides a flexible framework to detect age-independent and age-dependent effects of genetic variants on rates of structural brain changes. We identified genetic variants for structural brain changes between 4 and 99 years of age. Some of these were independent of age, showing effects that were stable throughout life in terms of strength and direction, suggesting that these genetic variants are equally crucial for early brain development as for brain ageing. In addition, we identified age-dependent genetic variants, suggesting that some genetic variants are predominantly associated with brain development while others are mainly associated with brain ageing.

Amongst our top findings is the *APOE* gene, a major risk factor for AD²³, and specifically a missense variant in that gene, which influences rates of change in amygdala and

hippocampus volume with varying and differential effects across the lifespan, with probably most pronounced effects in those affected with brain disorders. While most of the additional genetic loci identified here have not previously been associated with any brain-plasticity-related phenotypes, several others were also linked to brain disorders, including psychiatric (e.g., *GPR139* and *CDH8*) and neurodegenerative disorders (e.g., *NECTIN2*). Notably, *DACHI* and *NECTIN2* show increased expression during early development, while other genes' brain expression patterns are most pronounced during adulthood (e.g., *APOE* and *CDH8*), suggesting that these genes may exert specific effects during different developmental periods.

Gene-set analysis also implies a role for both developmental and neurodegenerative processes. We found a gene-set involved in 'neural nucleus development' that influenced rates of change in cerebellar white matter. Other closely related gene ontology terms, 'development of the substantia nigra and midbrain nuclei', were associated with rates of change of cerebral white matter volume and surface area. These all implicate the biological process of progression of a neural nucleus, a compact cluster of neurons in the brain, from its initial condition or formation to its mature state. This would also suggest that we observed the influence of genes involved in early developmental mechanisms of (subcortical) nuclei on cortical changes later in life. It is unclear whether this is a direct effect of these gene sets on cortical changes in adulthood, or the consequence of these early developmental pathways. In addition, we found several gene-sets interacting with tau-protein associated with rate of change in caudate volume, and a gene-set associated with rate of change in surface area that implicates phorbol 13-acetate 12-myristate, an activator of protein kinase C (PKC)²⁵. PKC is a family of enzymes whose members transduce a large variety of cellular signals and plays a key role in controlling the balance between cell survival and cell death. Its loss of function is generally associated with cancer, whereas its enhanced activity is associated with neurodegeneration. PKC both directly phosphorylates tau and indirectly causes the dephosphorylation of tau, and has been suggested to play a key role in the pathology of Alzheimer's disease³⁵. Together these results suggest involvement of genes in ageing and neurodegeneration.

At the global, genome-wide level, we found significant genomic overlap between genetic variants associated with rate of change with genetic variants associated with depression, schizophrenia, cognitive functioning, insomnia, height, body mass index (BMI) and ever-smoking. Several of these traits, such as schizophrenia, smoking, cognitive functioning, and body mass index, have been associated with longitudinal brain-structural changes^{5,36-38}. The global overlap coincides with findings at the individual gene level: several of the identified genetic variants and genes were linked to metabolic processes (*APOE*, *DACHI*, *GPR139*, *NECTIN2*), cognitive functioning (*CDH8*), psychiatric traits (*GPR139*, *SORCS2*, *CDH8*) and Alzheimer's disease (*NECTIN2* and *APOE*) as apparent from the pheWAS results. Despite the pleiotropic effects, concordance of effects was generally null. This is not surprising, as rate-of-change measures for brain structures are not constant and often switch sign over the course of the lifespan^{1,39}, whereas the GWAS for other traits assume stability of both the phenotype and the genetic influences on the phenotype over time. As such, concordance and discordance of effects would not be expected.

The advantage of longitudinal analyses is that each individual acts as their own control, allowing us to separate the genetic effects on volumes in cross-sectional studies from those on the rates of change¹⁴. Indeed, we found little overlap between the two: top genes identified in the GWAS on cross-sectional brain structure^{26,40–42} generally did not overlap with the top genes for the corresponding rates of change. Longitudinal analyses have long been shown to provide different information from cross-sectional approaches. On a phenotypic level, ageing patterns of the hippocampus show different results in cross-sectional studies than in longitudinal studies⁴³. On a genetic level, a study that included a within-sample SNP-by-age interaction in the ADNI cohort showed that the power to detect genetic associations was larger for a longitudinal design than for a cross-sectional analysis⁴⁴. Of note, that study also identified rs429358 in *APOE* as being associated with longitudinal hippocampal and amygdala volume change in older age (the ADNI cohort is also included in the current study). Through our meta-regression approach, we now show this variant to exert an effect across the lifespan, with the risk variant for AD causing faster increases in childhood for amygdala volume and faster volume reductions for both amygdala and hippocampus later in life.

Given the dynamics of brain structural changes during the lifespan, we investigated both age-independent and age-dependent genetic effects. The age-independent effects can be interpreted as neurodevelopmental influences that also impact brain structure at older ages^{45,46}, whereas the age-dependent effects can be interpreted as possible changing effects of genes or gene expression during life¹⁶. The genome-wide meta-regression approach employed here may enable future GWAS for other phenotypes that change over the human lifespan.

We chose to analyse longitudinal changes for 15 separate brain structures, because we observed generally low correlations between these phenotypic changes. This approach allowed us to find brain-structure-specific associations. However, several longitudinal studies have described phenotypic correlations between structural changes^{39,47,48}; combining several phenotypes could thus be an alternative approach to identify genetic variants that exert a global effect. Of note, cohort and age are intertwined in our meta-regression analysis. Although the cohorts analysed in this study together cover the full lifespan, there is relatively little age overlap between them; therefore, we cannot be sure that differences between cohorts can be exclusively attributed to age. Mega-analysis would circumvent this problem, but was not feasible in practice. Moreover, we imposed the same stringent criteria of genome-wide significance for the age-independent meta-analysis and age-dependent meta-regression, which renders chance findings equally unlikely in either type of analysis. In addition, residual heterogeneity for the top findings was generally small. That said, our sample size is still relatively modest for GWAS purposes, and replication in larger samples and inclusion of other ancestries is needed once more longitudinal data becomes available.

How exactly variation in these genes impacts brain changes in health and disease cannot be answered based on genome-wide association studies. To this end, our findings may direct future studies into brain development and ageing, and prevention and treatment of brain disorders. For example, biological pathways that guide neural nucleus development in the

foetal subcortical brain may be particularly relevant to the cerebral white matter growth and cortical thinning that takes place during childhood and adolescence. Neurodegenerative disorders might be better understood when we identify genetic variants that influence brain atrophy over time, compared with identification of static genetic differences. In conclusion, our study shows that our genetic architecture is associated with the dynamics of human brain structure throughout life.

Methods

Ethical approval

All participants gave written informed consent and all participating sites obtained approval from local research ethics committees/institutional review boards. Ethics approval for meta-analyses within the ENIGMA consortium was granted by the QIMR Berghofer Medical Research Institute Human Research Ethics Committee in Australia (approval: *P2204*).

Inclusion criteria

Cohorts that had longitudinal magnetic resonance imaging (MRI) data of the brain and genotyped data extracted from blood or saliva available were invited to participate, irrespective of disease status and age. Patients were not excluded as aberrant brain trajectories are often observed and we hypothesize that genetic risk for disease may be associated with genetic influences on rates of change. We included cohorts that had a preferred sample size of at least 75 subjects and a follow up duration (for repeated MRI scans) of at least six months. After quality control of individual subject's imaging and genotyping data, not all the cohorts could meet these criteria. In total, we included 15,640 subjects aged 4 to 99 (49% female, 14% patients). Please see Extended Data Fig. 1 and Supplementary Table 1 for further description of the cohorts.

Longitudinal imaging

Eight global brain measures (total brain including cerebellum and excluding brainstem, surface area measured at the grey-white matter boundary, average cortical thickness, total lateral ventricle volume, and cortical and cerebellar grey and white matter volume) and seven subcortical structures (thalamus, caudate, putamen, pallidum, hippocampus, amygdala and nucleus accumbens) were extracted from the FreeSurfer processing pipeline^{49–51}; see Supplementary Table 2 for details per cohort). We chose these measures based on the fact that they show generally high test-retest reliability for cross-sectional measures^{52–54}, thereby selecting those measures that would have sufficient signal to noise in change measures. Image processing and quality control were performed at the level of the cohorts, following harmonized protocols (<http://enigma.ini.usc.edu/protocols/imaging-protocols/>) which included visual inspection of the segmentation. Annual rates of change were computed in each individual for each phenotype by subtracting baseline brain measures from follow up measures and dividing by the number of years of follow-up duration. We chose not to correct for overall head size in the main analysis: while it is common practice to correct for intracranial volume when investigating cross-sectional brain volumes⁵⁵, the associations between intracranial volume and brain changes over time are small (Extended Data Fig. 2) and GWAS findings are very similar with and without correction

(Supplementary Note; Supplementary Figure 8). Distributions of baseline and follow-up measures - as well as annual rates of changes - were visually inspected and change rates were centrally compared for consistency.

Longitudinal trajectories of brain structure rates of change were estimated by applying locally, cohort-size weighted, estimated scatterplot smoothing with a Gaussian kernel, local polynomials of degree 2 and a span of 1 (LOWESS⁵⁶) implemented in R⁵⁷. Integrating these trajectories and then fitting these to the baseline values of the phenotypes in the cohorts provides trajectories throughout the lifespan. Trajectories were estimated in the full dataset including patients and by excluding diagnostic groups in each cohort separately.

Genome-wide association analysis

At each participating site, genotypes were imputed using the 1000 Genomes project dataset⁵⁸ through the Michigan imputation server⁵⁹ (<https://imputationserver.sph.umich.edu/>) or the Sanger imputation server⁶⁰ (Supplementary Table 3). Subsequently, each site ran the same multidimensional scaling (MDS) analysis protocol, computing MDS components from the combination of their cohort's data with the HapMap3 population⁶¹. This ensured that all sites corrected for ancestry in a consistent manner. See <http://enigma.ini.usc.edu/protocols/genetics-protocols/> for the imputation and MDS analysis protocol. Within each cohort genome-wide association was conducted using an additive model, modelling change rate as a function of the genetic variant plus covariates age, sex, age*sex, age², age²*sex and ancestry (the first four MDS components). While it is possible that rates of brain structural changes are different in males and females, we did not have the power to perform analyses separating the sexes. Dummy variables were added where appropriate, e.g., when multiple scanners were used. We re-ran these analyses adding a covariate for disease status if the cohorts contained patients and controls. Most sites used our harmonized GWAS protocol, which used *raremetalworker*⁶² for analysis (Supplementary Table 3). Regardless of the study design, a kinship matrix was incorporated in these analyses, accounting for relatedness in family studies, or possible unknown kinship in the other studies.

Given the small sample sizes of the individual cohorts, a stringent cohort level quality control was enforced, to exclude variants with a minor allele frequency (MAF) < 0.05 or variants with imputation R² / info score < 0.75. Across cohorts and phenotypes, GWAS summary plots (Manhattan plots and QQ plots) were visually inspected at the central site. If a given cohort / trait showed deviation from expectations, sites were asked to re-analyse their data, which usually involved removal of outliers in the phenotypic data. QQ plots per cohort, per phenotype can be found in Supplementary Figure 10.

Meta-analysis and Meta-regression

In the phase 1 cohorts of European ancestry (N=9,604) we aggregated the cohort-level data for each phenotype, using standard-error weighted meta-analysis or meta-regression. We employed a cumulative meta-analysis and meta-regression approach for replication, in phase 2 (N=15,100). The meta-regression could not be performed separately in the three independent cohorts added in phase 2 since a regression line based on three points is

prone to overfitting. For age-independent analyses, we list results in the added sample (Supplementary Tables 4 and 10). We tested three models. Under the assumption that effect sizes of single nucleotide polymorphisms (SNPs) were consistent across the lifespan (i.e., a standard meta-analytic approach), where the subscript C denotes a cohort and ϵ an error term:

1. $\text{Effect_SNP}_C \sim b_0 + \epsilon_c$, under the null hypothesis that $b_0 = 0$.

Given that brain changes throughout life are dependent on age, the effects of a genetic variant on brain change are likely to depend on age too. Within cohorts, such an age by SNP effect analysis would not have been feasible since longitudinal cohorts that span the age-range between 4–99 years do not exist. Given the widespread mean age among the cohorts included (Extended Data Fig. 1 and Supplementary Table 1), it was possible to calculate the age-dependent effects across the life span by comparing effects of loci between cohorts, through meta-regression. Meta-regression is a sophisticated tool for addressing heterogeneity between cohorts in meta-analyses when the source of heterogeneity is known (in this case, age)⁶³. We estimated the following model under the assumption that the effects of SNPs may vary in size or direction across the lifespan:

2. $\text{Effect_SNP}_C \sim b_0 + b_1 \cdot \text{age}_c + \epsilon_c$ under the null hypothesis that $b_1 = 0$ (1 degree of freedom), and
3. $\text{Effect_SNP}_C \sim b_0 + b_2 \cdot \text{age}_c + \epsilon_c$ under the null hypothesis that $(b_1 = b_2 = 0, 2$ degrees of freedom).

SNP data were aligned using METAL⁶⁴ for all three analyses. The age-independent effect of SNPs (model 1) was computed in METAL. For the age-dependent analyses (model 2 for linear age effects and model 3 for quadratic age effects) the aligned data were imported into R⁵² and fixed effects meta-regression was performed using the R-package metafor⁶⁵ (version 2.0–0). Results were filtered on SNPs that were present for at least 50% of the cohorts and in at least 50% of the subjects.

Functional mapping

Functional mapping was performed using the FUMA platform designed for prioritization, annotation and interpretation of GWAS results⁶⁶. As the first step, independent significant SNPs in the individual GWAS meta-analysis summary statistics were identified based on their p -value ($p < 5 \times 10^{-8}$) and independence of each other ($r^2 < 0.6$ in the 1000G phase 3 reference) within a 1Mb window. Thereafter, lead SNPs were identified from independent significant SNPs, which are independent of each other ($r^2 < 0.1$). We used FUMA to annotate lead SNPs in genomic risk loci based on the following functional consequences on genes: eQTL data (GTEx v6 and v7⁶⁷), blood eQTL browser⁶⁸, BIOS QTL browser⁶⁹, BRAINEAC⁷⁰, MuTHER⁷¹, xQTLServer⁷², the CommonMind Consortium⁷³ and 3D chromatin interactions from HI-C experiments of 21 tissues/cell types⁷⁴. Next for eQTL mapping and chromatin interaction mapping, genes were mapped using positional mapping, which is based on a maximum distance between SNPs (default 10kb) and genes. Chromatin interaction mapping was performed with significant chromatin interactions (defined as $\text{FDR} < 1 \times 10^{-6}$). The two ends of significant chromatin interactions were

defined as follows: region 1 – a region overlapping with one of the candidate SNPs, and region 2 – another end of the significant interaction, used to map to genes based on overlap with a promoter region (250bp upstream and 50bp downstream of the transcription start site).

Visualization of SNP effects

We visualized the effects of our top SNPs on the lifespan trajectory, assuming no effects of the other SNPs, for easier interpretation of the direction of effect. Similar to the estimation of the lifespan trajectory, we estimated a smoothed version $f(x)$ of the phenotypic change rate using LOWESS (see above) and integrated the rate of change. We added the unknown volume C at the start of our age range by fitting the integrated curve to the baseline data. Suppose $h(x)$ is the unknown rate of change for non-carriers. The additional change rate $g(x)$ for carriers was estimated through the meta-analysis or meta-regression. The full dataset contained a fraction p of the carriers of the tested allele. Assuming $p + q = 1$, $f(x) = p * (h(x) + g(x)) + q * h(x) = h(x) + p * g(x)$. We created a rate of change curve for non-carriers as $f(x) - p * g(x)$ and a rate of change curve of carriers as $f(x) + q * g(x)$. The offset C is potentially different in carriers and non-carriers, so we estimated this difference by taking the effect of the cross-sectional GWAS data (see below) in this SNP, or a proxy SNP in high linkage disequilibrium (LD).

Gene-based and gene-set analyses

Gene-based associations with 15 phenotypes were estimated using MAGMA⁷⁵ (version 1.09a) using the summary statistics from age-independent and age-dependent GWAS meta-analyses of rate of change of global brain measures. Gene names and locations were based on NCBI 37.3 locations as provided by MAGMA. Association was tested using the SNP-wise mean model, in which the sum of $-\log(\text{SNP } p\text{-value})$ for SNPs located within the transcribed region was used as the test statistic. LD correction was based on estimates from the 1000 Genomes Project Phase 3 European ancestry samples⁵⁸. To describe the direction of the age effect for significant genes in the age-dependent analyses, we subsequently identified the SNPs that were used in the gene-based p -value and plotted the age-dependent effect of the top SNP that contributed to the gene-based p -value.

The generated gene-based p -values were used to analyse sets of genes in order to test for association of genes belonging to specific biological pathways or processes. MAGMA applies a competitive test to analyse if the genes of a gene set are more strongly associated with the trait than other genes, while correcting for a series of confounding effects such as gene length and size of the gene set. For gene sets we used 9,975 sets with 10 –1,000 genes from the Gene Ontology sets⁷⁶ curated from MsigDB 7.0⁷⁷.

Multiple testing corrections

We investigated annual rates of change for 15 brain phenotypes, but these are correlated to some extent (Extended Data Fig. 2). We therefore estimated the effective number of independent variables based on matrix spectral decomposition⁷⁸ for the largest adolescent cohort (IMAGEN; N=1,068) and for the largest elderly cohort from the phase 1 sample (ADNI2; N=626). The most conservative estimate of the number of independent traits was

13.93. Despite the fact that models 2 and 3 are nested and therefore not independent, we also corrected for performing three analyses per trait. The study-wide significant threshold for the genome was therefore set at $p < 1.2e-09$ ($5e-08/13.93*3$). For gene-based significance, we applied a genome-wide significance level of $0.05/17541 = 2.85e-06$, and a study wide significance of $2.85e-06/(13.93*3)$, i.e. $p < 6.82e-08$. For gene-set significance, we applied a genome-wide significance level of $0.05/9,975 = 5.01e-06$ and a study-wide significance level of $5.01e-06/(13.93*3)$, i.e. $p < 1.20e-07$.

SNP heritability

SNP heritabilities, h^2_{SNP} , were estimated by using linkage disequilibrium (LD) score regression⁷⁹ (LDSR) for the European-ancestry brain change GWASs to ensure matching of population LD structure. For LDSR, we used precomputed LD scores based on the European-ancestry samples of the 1000 Genomes Project⁵⁸ restricted to HapMap3 SNPs⁶¹. The summary statistics with standard LDSC filtering were regressed onto these scores. SNP heritabilities were estimated based on the slope of the LD score regression, with heritabilities on the observed scale calculated. To ensure sufficient power for the genetic correlations, r_g was calculated if the Z-score of the h^2_{SNP} for the corresponding GWAS was 4 or higher⁷⁹.

Comparison with cross-sectional results

For the genome-wide significant genes and genes associated with genome-wide significant SNPs, we compared our findings with cross-sectional GWAS summary statistics when available. To this end, datasets^{26,40–42} were requested and downloaded from <http://enigma.ini.usc.edu/research/download-enigma-gwas-results/> and http://big.stats.ox.ac.uk/download_page. Gene-based association analyses for cross-sectional brain GWAS summary statistics were performed using MAGMA (as described above). Additionally, we compared the overlap in the first 1,000 ranked genes to the expected number of overlapping genes based on chance. False discovery rate correction⁸⁰ was applied to determine over- or under-representation of genes from our longitudinal GWAS to the cross-sectional previously published GWAS^{26,40–42}.

Overlap with cross-sectional results and other traits

To investigate genetic overlap with other traits across the genome we applied an adapted version of iSECA⁸¹ (independent SNP effect concordance analysis) which examines pleiotropy and concordance of the direction of effects between two phenotypes by comparing expected and observed overlap in sets of SNPs from both phenotypes that are thresholded at different levels. From the results at each threshold, heatmap plots were generated containing binomial tests for pleiotropy and Fisher's exact tests for concordance. An empirical p -value for overall pleiotropy and concordance was then generated through permutation testing. Our implementation of iSECA also included a p -value for overall discordance, as we expect some phenotypes to negatively influence brain-structural change rates. P -values were computed using a two-step approach: we first ran 1,000 permutations. If the p -value for pleiotropy was below $0.05/15$ we reran the analyses with 10,000 permutations to obtain a more precise p -value. Summary statistics of change rates were first filtered on SNPs for which $> 95\%$ of the subjects contributed data to remove the sample size

dependency of p -values and subsequently clumped ($p=1, kb=1000$) to ensure independence of input SNPs.

We investigated the genetic overlap between brain-structural changes and risk for 20 neuropsychiatric, neurological and somatic disorders, and physical and psychological traits. Summary statistics were downloaded or requested for aggression⁸², alcohol dependence⁸³, Alzheimer's disease⁸⁴, attention-deficit/hyperactivity disorder⁸⁵, autism⁸⁶, bipolar disorder⁸⁷, body mass index³⁰, brain age gap¹², cognitive functioning²⁹, depression²⁷, diabetes type 2⁸⁸, ever-smoking³², focal epilepsy⁸⁹, height³⁰, inflammatory bowel disease⁹⁰, insomnia³¹, multiple sclerosis⁹¹, Parkinson's disease⁹², rheumatoid arthritis⁹³ and schizophrenia²⁸. These phenotypes were chosen because of known associations with brain structure or function, and availability of summary statistics based on large GWA-studies. For comparison, we computed the genetic overlap between cross-sectional brain structure and these phenotypes, using the same method.

Apart from these, we also 1) included intracranial volume⁹⁴ to investigate the effect of overall head size and 2) tested the overlap between each structure's longitudinal change measure against its cross-sectional brain structure. Pleiotropy, concordance or discordance was considered significant when the p -value was smaller than $0.05/15*22$ (#change rates * #phenotypes tested) = $1.5e-04$.

Brain gene expression

GENE2FUNC, a core process of FUMA⁶⁶ (Functional Mapping and Annotation of Genome-wide Association Studies), was employed to analyse gene expression patterns. For this, a set of 8 genes was used as input, including all genome-wide significant genes and genes harbouring genome-wide significant SNPs (compare Supplementary Tables 5,7,9,11). Gene expression heatmap was constructed employing GTEx v8³³; 54 tissue types) and BrainSpan RNA-seq data across 29 different ages or 11 different developmental stages³². The average of normalized expression per label (zero means across samples) was displayed on the corresponding heatmaps. Expression values are TPM (Transcripts Per Million) for GTEx v8 and RPKM (Read per Kilobase Million) in the case of the BrainSpan data set.

Phenome-wide association studies

To identify phenotypes associated with the candidate SNPs and genes (defined as genome-wide significant SNPs and the genome-wide significant genes and genes associated with genome-wide significant SNPs), a phenome-wide association study (pheWAS) was done for each SNP and/or gene. PheWAS was performed using public data provided by GWASAtlas³²(<https://atlas.ctglab.nl>). To correct for multiple testing, the total number of GWASs (4,756) was considered (including GWASs in which the searched SNP or gene was not tested) and the number of tested SNPs and genes ($n=14$), resulting in a Bonferroni corrected p -value threshold of $1.05e-05/14$, i.e., $p < 7.51e-07$.

Sensitivity analyses

The phase 2 analyses include available data from all cohorts with European ancestry ($N=15,100$). The four cohorts of non-European and mixed ancestry together consist of

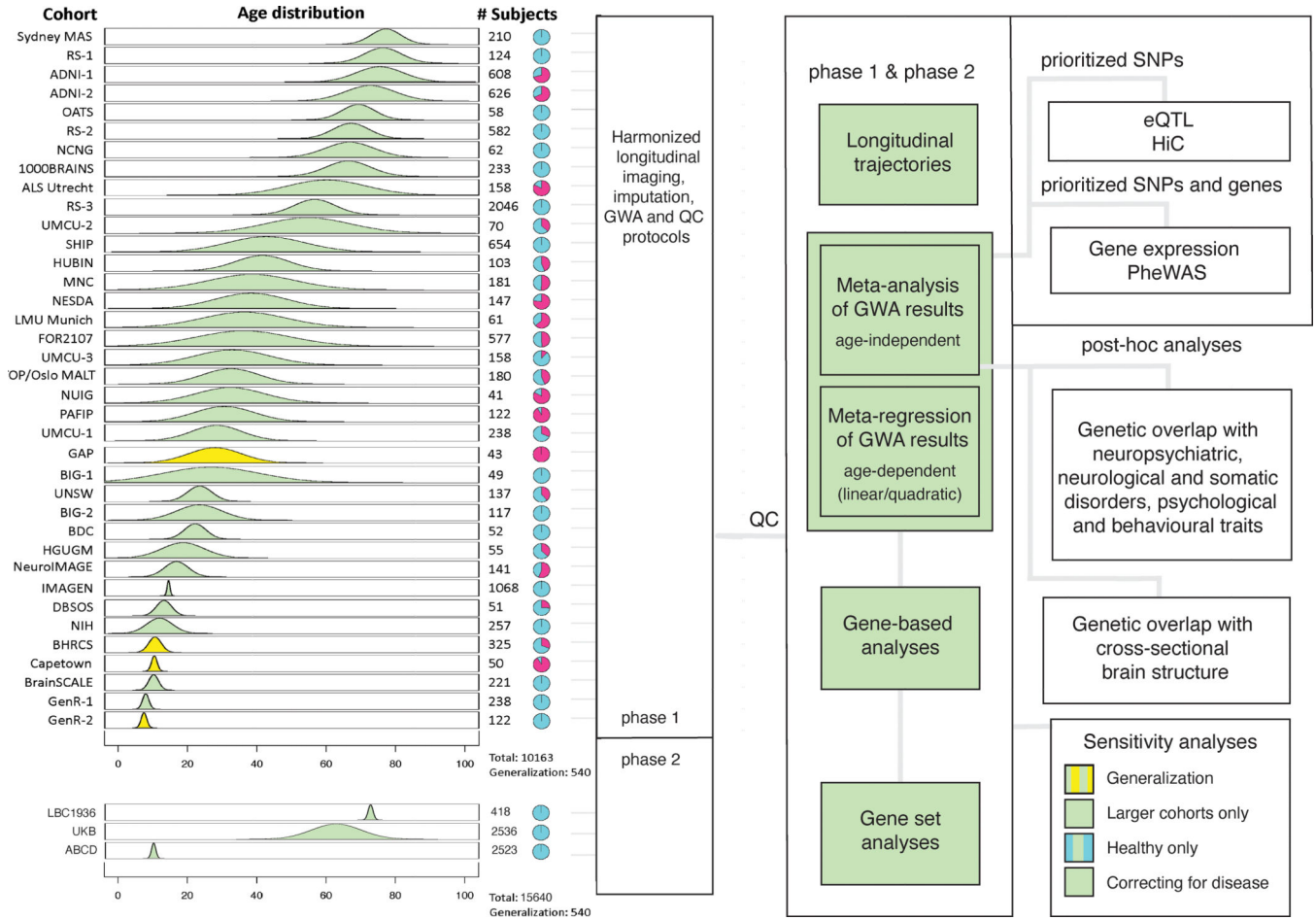
540 subjects, who are predominantly children and adolescents (Supplementary Table 3). The number of subjects, heterogeneity in ancestry and the age-distribution do not allow for separate meta-analysis or meta-regression. We therefore added the cohorts of non-European ancestry to the original datasets and reran analyses (N=15,640). In a second analysis, we excluded the 9 cohorts that had N < 75 or mean scanning interval < 0.5 years (Supplementary Table 2), leaving N=14,601 subjects. The main analyses include data from all subjects combined, without correction for disease. This approach was chosen because many neurological and neuropsychiatric diseases are characterized by aberrant brain changes over time, and genes involved in the disease may also be involved in these brain changes. To check whether our results were confounded by disease, we repeated the main analyses excluding diagnostic groups of each cohort (N=13,0349) and by correcting for disease status.

Data availability:

This work is a meta-analysis. Upon publication, the meta-analytic results will be made available from the ENIGMA consortium webpage (<http://enigma.ini.usc.edu/research/download-enigma-gwas-results>). Cohort level data can be shared upon request, after permission of cohort principal investigators. Individual level data can be shared with interested investigators, subject to local and national ethics regulations and legal requirements that respect the informed consent forms and national laws of the country of origin of the persons scanned. Figures that contain cohort level (meta) data: Figures 1, 2, Extended data Figures 1,2, Supplementary Figures 1,3,8,10.

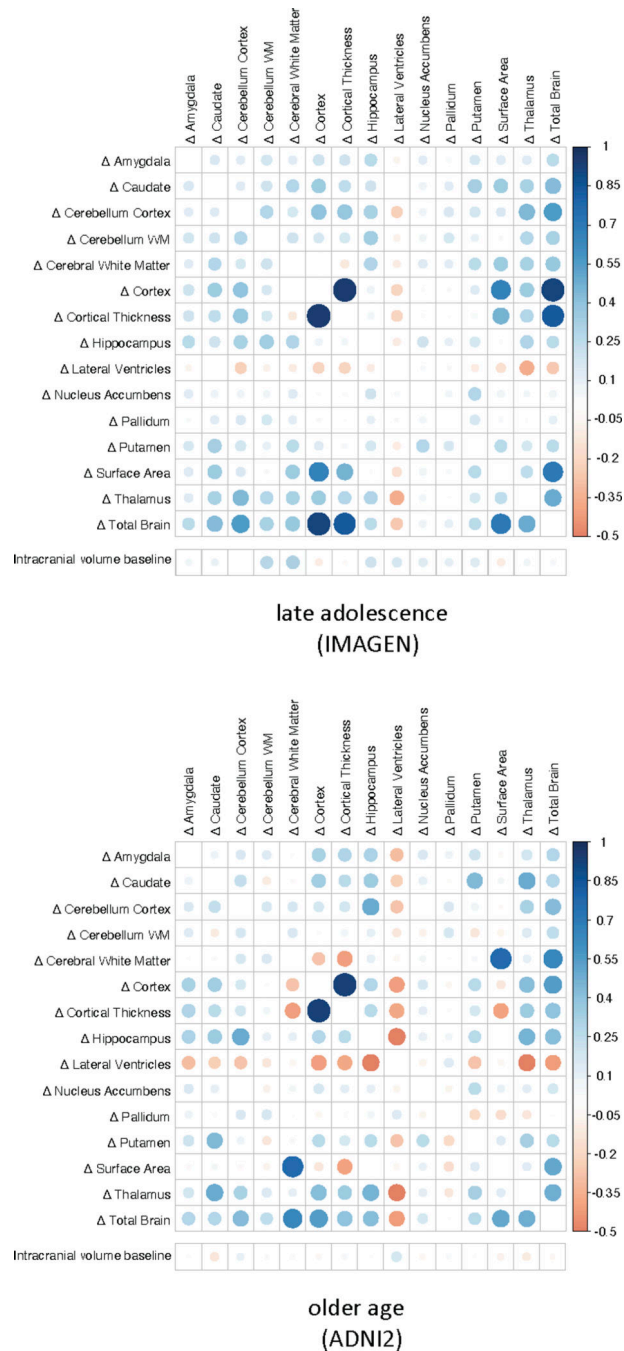
Public data used in this work include the ABCD cohort (data release 3.0, accessible through <https://nda.nih.gov/abcd>; <http://dx.doi.org/10.15154/1519007>), ADNI cohort (accessible through adni.loni.usc.edu), and the UK biobank cohort (data request 11559, <https://www.ukbiobank.ac.uk>).

Extended Data



Extended Data Fig. 1. Demographics and analysis

Overview of demographics (left). Per cohort, an age distribution is displayed, based on mean and standard deviation of the age at baseline. Cohorts of European ancestry are displayed in green, non-European cohorts are displayed in yellow. On the right, the total number of included subjects is displayed and a pie-chart of the distribution of diagnostic groups (pink) and subjects not belonging to diagnostic groups - often healthy subjects (aqua). Overview of analysis pipeline (right).



Extended Data Fig. 2. Correlations between change rates

Pearson correlations between rates of change and between baseline intracranial volume and rates of change in the largest adolescent cohort (top, N = 1068) and the largest cohort in older age (bottom, N = 624) in phase 1. The size of the correlations is displayed by color and size of the circles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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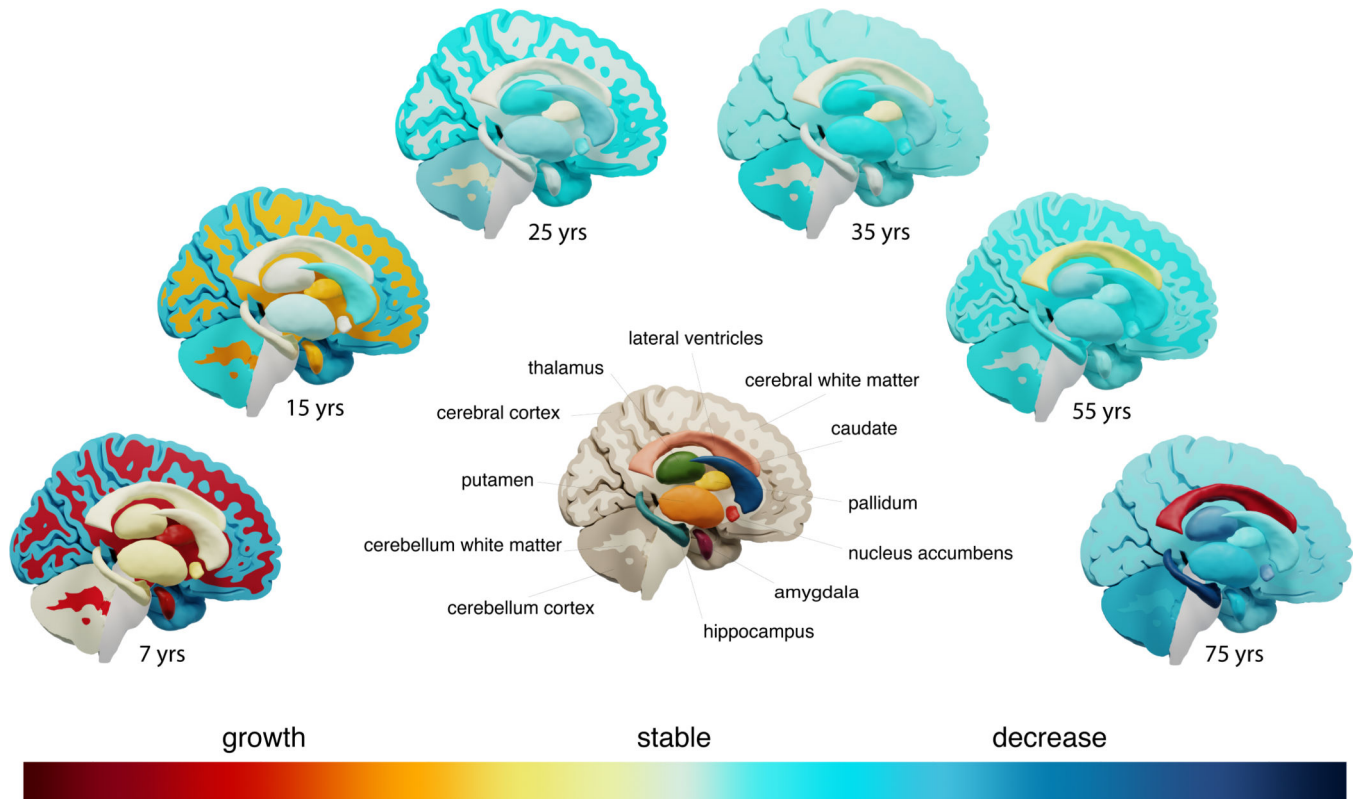


Figure 1:
 Phenotypic brain changes throughout the lifespan.
 Visualization of growth and decline of brain structures throughout the lifespan. The subcortical structures are shown in exploded view.

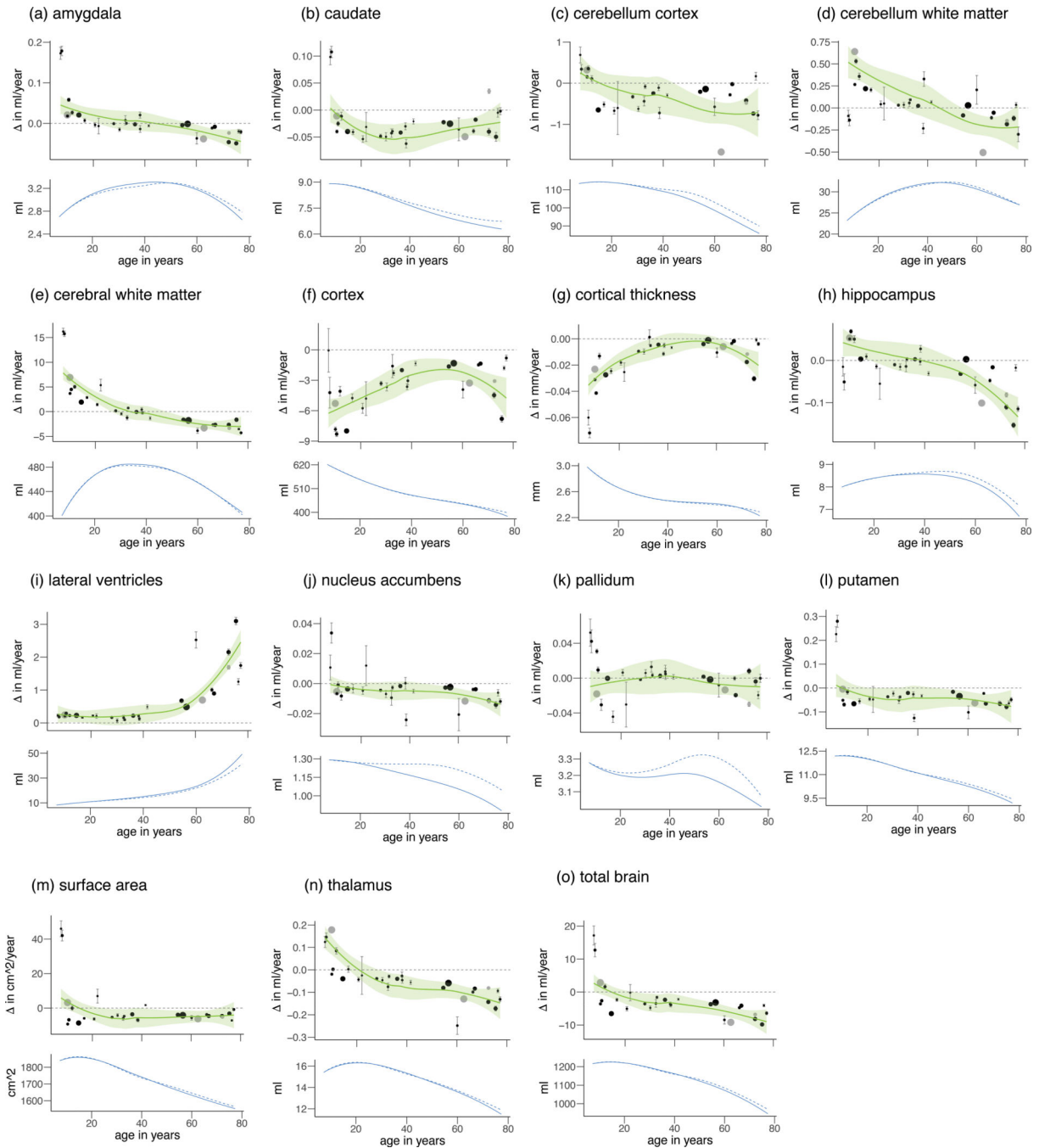


Figure 2: Annual rates of change per cohort for each structure (a-o). The estimated trajectories with 95% confidence intervals (*in green*) are displayed in the top row. Mean values of individual cohorts are displayed as points, with error bars representing standard errors displayed in grey. The size of the points represents the relative size of the cohorts, total sample size N=15640. Means and standard deviations are based on raw data – no covariates were included. Cohorts that were added in phase 2 are displayed in grey. Only cohorts that satisfy N>75 and mean interval > 0.5 years are shown. The estimated

trajectories of the volumes themselves are displayed in the bottom row, for all subjects (*solid line*) and for subjects not part of diagnostic groups (*dashed line*).

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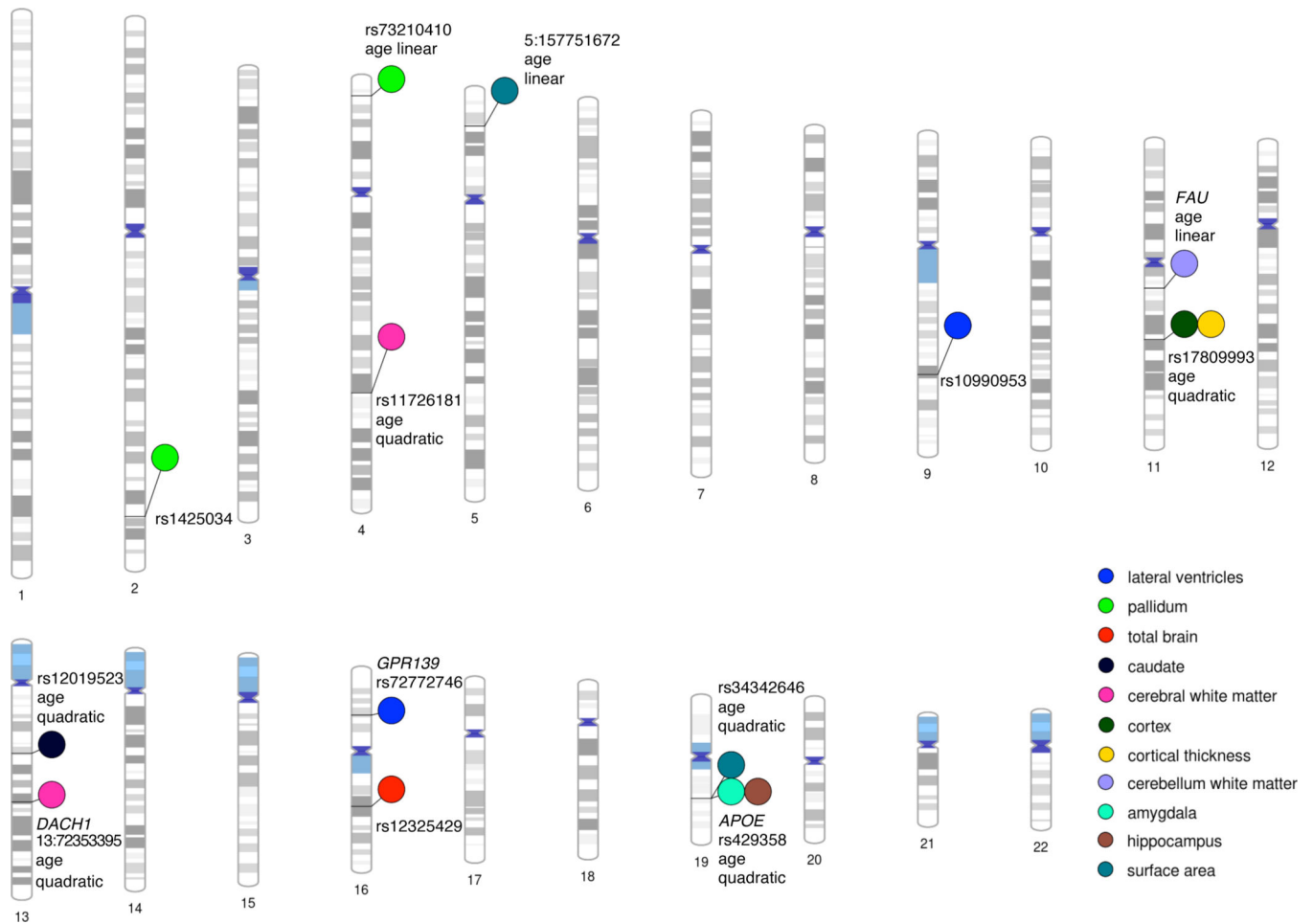


Figure 3: Genetic effects on rates of brain changes throughout the lifespan. Genome-wide significant SNPs and genes with effects on brain changes at their respective loci across the human genome, from phase 2 (total N=15,100). This plot was created using PhenoGram (<http://visualization.ritchielab.org>).

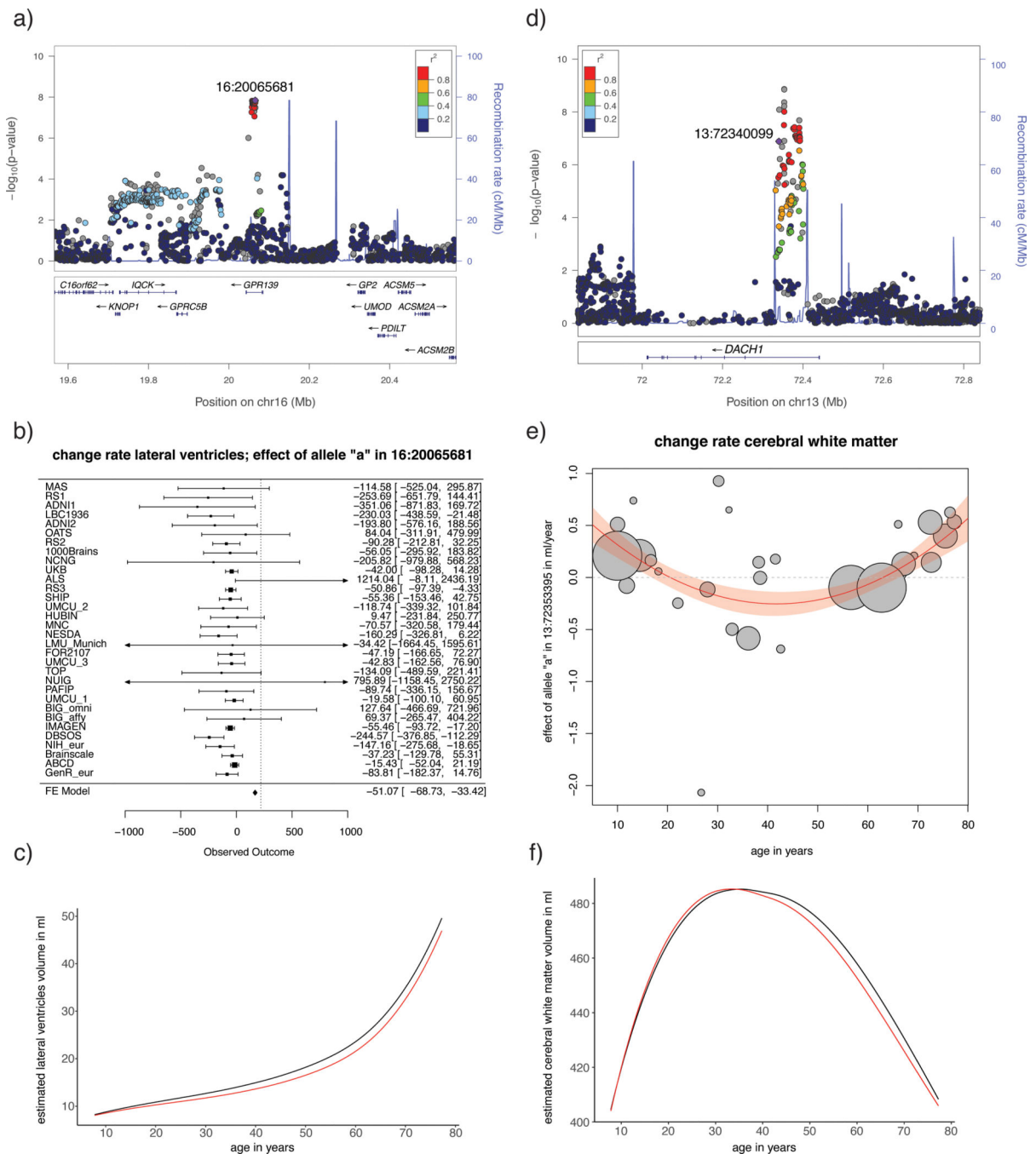


Figure 4: Summary of findings for two top-SNPs. Shown here is a summary of findings for a top-SNP of an age independent effect (rs72772746; intron to *GPR139*; associated with rate of change of lateral ventricle volume; left column) and a top-SNP of an age dependent effect (13:72353395; intron to *DACH1*; associated with rate of change in cerebral white matter volume; right column). Displayed are the locus plots (a) and (d), forest plot (b; total N = 14593, means and 95% confidence intervals are displayed for each cohort; confidence intervals that are outside the axis of the

plot are marked with an arrow) and plot of meta-regression (e; total $N = 13864$, center of the circles represent the effect size of the tested allele for each cohort, radius of the circles are proportional to sample size) and inferred lifespan trajectories for carriers (in red) and non-carriers of the effect allele (in black) (c) and (f). Note that 13:72353395 was not in the reference dataset containing LD structure; the displayed LD structure is based on 13:7234009, $R^2 = 0.87$ with the top-SNP.

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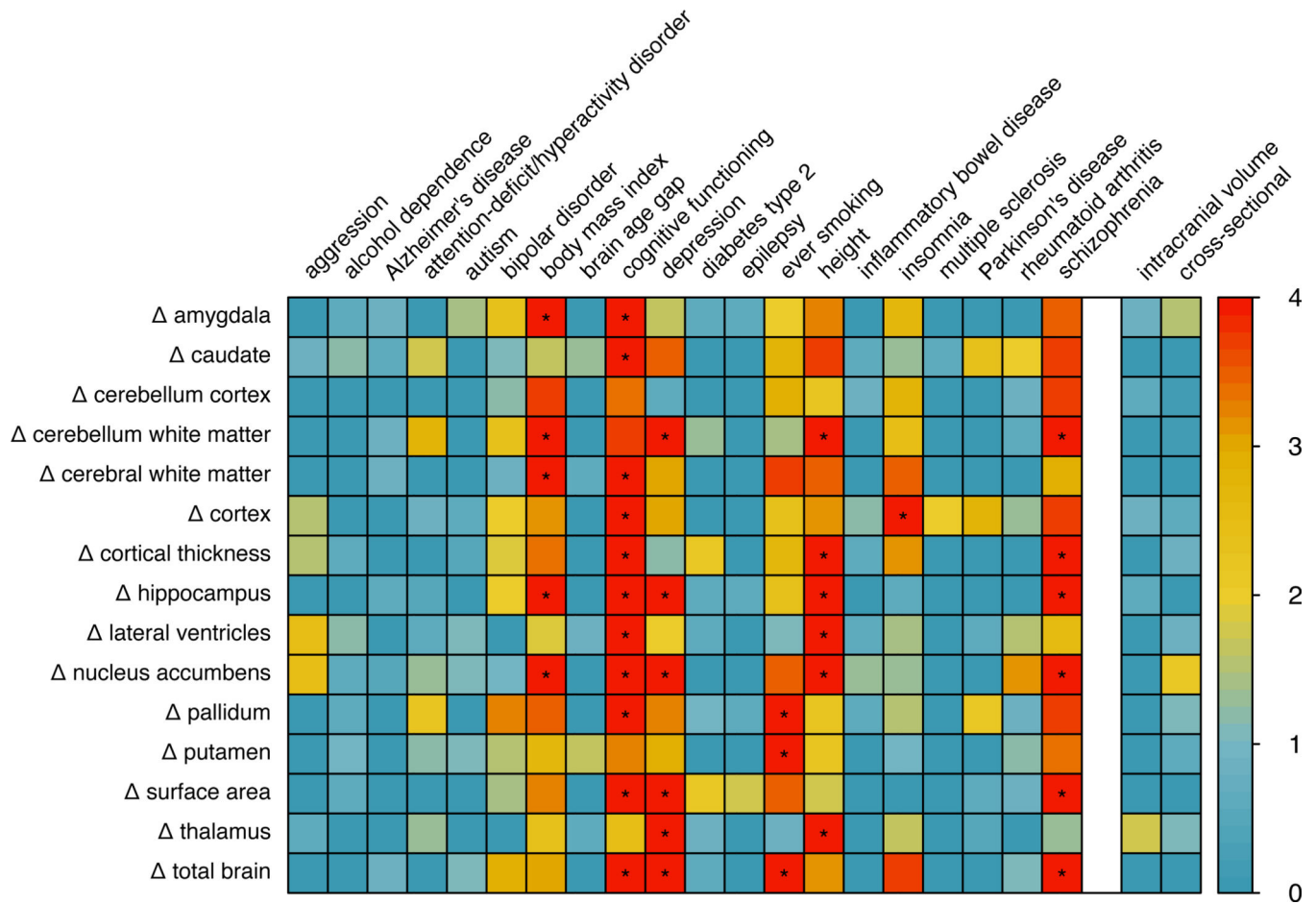


Figure 5: Genetic overlap with other phenotypes. *P*-values for pleiotropy between change rates of structural brain measures (rows, indicated by Δ for change rate) and neuropsychiatric, disease-related and psychological traits (columns on the left). *P*-values for pleiotropy between change rates of structural brain measures and head size (intracranial volume) and the cross-sectional brain measure are displayed on the right. The colour legend is displayed on the right, indicating the $-\log_{10}$ *p*-value. Significant overlap ($p < 1.6 \times 10^{-4}$; obtained through permutation testing, two-sided, Bonferroni corrected) is marked with *. *P*-values underlying this figure can be found in Supplemental Table 16.