

Title: Dynamics of Brain Structure and its Genetic Architecture over the Lifespan

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One-sentence summary

We identified common genetic variants associated with the rate of brain development and aging, in longitudinal MRI scans worldwide.

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. While heritable, specific loci in the genome that influence these rates are largely unknown. Here, we sought to find common genetic variants that affect rates of brain growth or atrophy, in the first genome-wide association analysis of longitudinal changes in brain morphology across the lifespan. Longitudinal magnetic resonance imaging data from 10,163 individuals aged 4 to 99 years, on average 3.5 years apart, were used to compute rates of morphological change for 15 brain structures. We discovered 5 genome-wide significant loci and 15 genes associated with brain structural changes. Most individual variants exerted age-dependent effects. All identified genes are expressed in fetal and adult brain tissue, and some exhibit developmentally regulated expression across the lifespan. We demonstrate genetic overlap with depression, schizophrenia, cognitive functioning, height, body mass index and smoking. Several of the discovered loci are implicated in early brain development and point to involvement of metabolic processes. Gene-set findings also implicate immune processes in the rates of brain changes. Taken together, in the world's largest longitudinal imaging genetics dataset we identified genetic variants that alter age-dependent brain growth and atrophy throughout our lives.

Introduction

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 changes (Hedman et al., 2012). Longitudinal studies are crucial to identify genetic and environmental factors that influence the rate of these brain changes throughout development (Giedd et al., 1999; Gogtay et al., 2004; Shaw, Gogtay, & Rapoport, 2010) and aging (Raz et al., 2005). Inter-individual differences in brain development are associated with general cognitive function (Ramsden et al., 2011; Schnack et al., 2015; Oschwald et al., 2019), and risk for psychiatric disorders (Shaw et al., 2009; Liberg et al., 2016) and neurological diseases (Reiter et al., 2017; Eshaghi et al., 2018; Jiskoot et al., 2019). Genetic factors involved in brain development and aging overlap with those for cognition (Brans et al., 2010; Brouwer et al., 2014) and risk for neuropsychiatric disorders (Brans et al., 2008). A recent cross-sectional study showed a genetic component to advanced brain age in

several brain disorders (Kaufmann et al., 2019). Yet, we still lack information on which genetic variants influence individual brain changes throughout life, since this requires longitudinal data. Discovering genetic factors for brain 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 aging worldwide.

As part of the Enhancing Imaging Genetics through Meta-Analysis (ENIGMA) consortium (Thompson et al., 2014; 2020), the ENIGMA Plasticity Working Group recently quantified the overall genetic contribution to longitudinal brain changes by combining evidence from multiple twin cohorts across the world (Brouwer et al., 2017). 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 aging. Even so, the genes involved in these processes are still not known. So far, only a single, small-scale genome-wide association study (GWAS) was performed for brain change (Szekely et al., 2018; N=715). 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. We performed a coordinated analysis of 37 longitudinal cohorts (N = 10,163, with a 3.5-year interval between scans on average, 22% of participants with a neurological or psychiatric diagnosis, 50% females, mainly of European descent (95%), aged 4 to 99 years (Supplementary Figure S1, Supplementary Tables S1-S3). Global and subcortical brain measures were extracted, and annual change rates were analyzed using additive genetic association analyses to estimate effects of genetic variants on rates of change within each cohort. As brain change is not constant over age (Hedman et al., 2012), and gene expression also changes during development and aging (Kang et al., 2011), we determined whether the estimated genetic variants were age-dependent, i.e., differentially affected rates of brain changes at different stages of life using genome-wide meta-regression models with linear or quadratic age effects (Materials and Methods).

Results

Longitudinal trajectories

Change in global brain measures showed different trajectories of change with age (Figure 1 and Supplementary Video), characterized by either monotonic increases (lateral ventricles), monotonic decreases (cortex volume, cerebellar

gray 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). Each brain structure showed a characteristic trajectory of change, as reflected by generally low correlation coefficients between rates of change (Supplementary Figure S2). Using the correlation structure, we estimated the effective number of independent variables through matrix spectral decomposition on the rates of change (Nyholt, 2004), yielding 14 independent traits for multiple testing corrections (Materials and Methods).

Age-independent associations with brain-structural change rates

Two loci showed genome-wide significant effects on the rate of brain change in cohorts of European ancestry (Table 1; Supplementary Figure S3 provides Manhattan plots, QQ plots, and locus plots; Supplementary Figure S4). The first lead SNP, rs72772740 on chromosome 16, is an intronic variant located in the *GPR139* gene and was associated with change in lateral ventricle volume (Figure 2). Functional annotation identified numerous significant eQTL associations (FDR < 0.05) in different datasets and highlighted genes by either eQTL mapping (*GPRC5B*, *IQCK*, *KNOP1*, *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 diseases (Nohr 2019). *GPR139* may play a role in fetal brain development (Süsens et al., 2006). The second lead SNP, rs449998, an intronic variant on chromosome 21 located in the Down Syndrome Cell Adhesion Molecule (*DSCAM*) gene, was associated with change in nucleus accumbens volume. Chromatin interactions highlighted *DSCAM* and additional genes as likely effector transcripts at this locus. *DSCAM* encodes a member of the immunoglobulin superfamily of cell adhesion molecules (Ig-CAMs), and is involved in the development of the human central and peripheral nervous system (Yamakawa et al., 1998). This gene has been identified in the critical Down syndrome region and is also a candidate risk gene for congenital heart disease (Agarwala et al., 2000).

Age-dependent associations with brain-structural change rates

The association of three additional loci with rate of change was variable across the lifespan (Table 1; Supplementary Figure S3 provides Manhattan plots, QQ plots, and locus plots; Supplementary Figure S4): white matter cerebellum volume change was affected by the intronic rs10674957 in the Thyrotropin Releasing Hormone Degrading Enzyme (*TRHDE*) gene, white matter cerebrum volume change was affected by rs573983368 (intronic variant) in the Dachshund Family Transcription Factor 1 (*DACH1*) gene, and rs6864758 (intergenic and located in long intergenic non-protein coding RNA

Table 1: SNPs for age-(in)dependent effect on longitudinal brain changes.

Phenotype (change rate)	SNP id	Chr	Position ^a	Tested Allele /Non-tested Allele	Frequency Tested Allele	Age-dependency model	Effect on change rate: Estimated model	P-value ^b	Gene in locus	Description of effect of tested allele ^c :
Surface Area*	rs6864758	5	157750349	a/g	0.6341	linear	-95.91 + 2.181 x age in mm ² /year	1.96e-08	intergenic; located in long intergenic non-protein coding RNA (LINC02227)	less growth in children, less decline in older age
Cerebellum White Matter	rs10674957	12	72717608	g/gagat	0.3051	linear	-47.49 + 1.242 x age in mm ³ /year	1.30e-08	intron variant, TRHDE	less growth in children, less decline in older age
Cerebral White Matter	rs573983368	13	72353395	a/g	0.3113	quadratic	899.15 - 56.726 x age + 0.683 x age ² in mm ³ /year	1.41e-09	intron variant, DACH1	more growth in children, less decline in older age
Lateral Ventricles	rs72772740	16	20064855	t/g	0.8841	constant	63.255 in mm ³ /year	1.06e-08	intron variant, GPR139	more growth over the whole lifespan
Nucleus Accumbens	rs449998	21	41467826	a/g	0.2423	constant	-1.954 in mm ³ /year	4.65e-08	intron variant, DSCAM	less growth in children, less decline in adults

^a Position based on build hg19. Data was clumped ($p < 1e-04$) to identify significant and LD-independent SNPs. ^bP-values are obtained by testing the age-independent effect versus no effect at all (age-dependency is "none") or age-related effects versus main effect only (age-dependency is linear – 1 degree of freedom - or quadratic – two degrees of freedom). *This locus also showed a genome-wide significant quadratic age effect. The most parsimonious model is listed in this table. Single significant SNPs without strong LD neighbors were omitted from this table. ^cSee Figure 1, Supplementary Figures S4 for the lifespan trajectories and a visualization of the effect of this locus.

LINC02227) on chromosome 5 had an age-dependent effect on the change in surface area (Figure 2; Table 1). Both the *TRHDE* and *DACH1* loci show significant chromatin interaction. *TRHDE* encodes a member of the peptidase M1 family. The encoded protein is an extracellular peptidase that specifically cleaves and inactivates the neuropeptide thyrotropin-releasing hormone (Bauer et al., 1999). Concurring with this, knockdown of *TRHDE* in *Drosophila* sensory neurons is known to result in altered cellular morphology, impaired nociception and the sensory response to (potentially) harmful stimuli (Nagy et al., 2015). In our study, carriers of the minor allele showed a slower increase of cerebellum white matter, followed by reduced decline in older age (Supplementary Figure S5). *DACH1* encodes a chromatin-associated protein that associates with DNA-binding transcription factors to regulate gene expression and cell fate determination during development. *DACH1* is highly expressed in the proliferating neuroprogenitor cells of the developing cortical ventricular and subventricular regions, and in the striatum (Castiglioni et al., 2019). We found the effect of *DACH1* to have a quadratic age-dependence, with the variant being associated with faster growth in childhood and earlier but slower decline with aging (Figure 2). To visualize the age-dependent effects, we plotted the meta-regression results for the significant loci (Materials and Methods, Supplementary Figure S5). The top-10 loci for each phenotype and age model are presented in Supplementary Tables S4 to S6.

Gene-based analyses

Gene-based associations with all phenotypes were estimated using MAGMA (version 1.07b; de Leeuw et al., 2015) based on summary statistics from our GWAS meta-analyses and meta-regressions. Gene names and locations were derived based on ENSG v92 (Zerbino et al., 2018). We found 15 genome-wide significant genes influencing structural rates of change (Table 2); among these, two genes reached study-wide significance, *GPR139* and *TMCO2*. *GPR139* was again associated with change in lateral ventricle volume in this analysis, and the Trans-Membrane and Coiled-coil domains 2 gene, *TMCO2*, was associated with an age-dependent change in thalamic volume. *DACH1* and *GPR39*, which were implicated through SNP-based GWAS, also reached genome-wide significance in this gene-based GWAS. Additional genome-wide significant findings included age-related effects of the Alzheimer's disease (AD)-related Apolipoprotein E gene (*APOE*) on change rates for both hippocampus and amygdala (Figure 2). Of note, this finding was 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 found that the effect of *APOE* on both phenotypes was fully driven by rs429358, with the risk variant for AD causing faster increases in childhood for amygdala and faster decay for both amygdala and hippocampus later in life (Figure 2). To visualize the age-dependent effects, we plotted the meta-regression results for the top SNP in each of the significant genes (Supplementary Figure S5). Supplementary Table S7 details putative biological functions of associated genes and genes harboring

Table 2: Genes contributing to longitudinal brain changes.

Phenotype (change rate)	Gene	Chr	Start position ^a	Stop position ^a	# independent SNPs	Age dependency	Z	P-value
Thalamus*	<i>TMCO2</i>	1	40711619	40717363	3	linear	5.410	3.14e-08
Cerebellum Gray Matter	<i>EPAS1</i>	2	46520806	46613836	18	constant	4.590	2.22e-06
Cerebellum Gray Matter	<i>PID1</i>	2	229715242	230136001	79	quadratic	4.697	1.32e-06
Cortical Thickness	<i>AC027309.1</i>	5	172036245	1720364361	1	linear	4.572	2.42e-06
Putamen	<i>TMEM30A</i>	6	75962640	75994684	3	constant	4.911	4.53e-07
Total Brain	<i>STEAP1B</i>	7	22459063	22672544	39	quadratic	4.815	7.36e-07
Cerebellum Gray Matter	<i>TMC1</i>	9	75136717	75451267	20	quadratic	4.708	1.25e-06
Cerebral White Matter	<i>DACH1</i>	13	72012098	72441330	21	quadratic	4.984	3.11e-07
Lateral Ventricles	<i>GPR139</i>	16	20042807	20085239	16	constant	5.724	5.20e-09
Cortex	<i>ABR</i>	17	906758	1132315	53	quadratic	4.626	1.86e-06
Cerebral White Matter	<i>MYOCD-AS1</i>	17	12626199	12661542	10	linear	4.709	1.24e-06
Caudate	<i>PLCD3</i>	17	43186335	43210721	13	linear	4.692	1.35e-06
Cerebellum White Matter	<i>OR7D2</i>	19	9296279	9299493	2	linear	4.637	1.77e-06
Amygdala	<i>APOE</i>	19	45409011	45412650	2	linear	4.607	2.05e-06
Hippocampus	<i>APOE</i>	19	45409011	45412650	2	quadratic	4.889	5.07e-07

^a Position based on build hg19. Study-wide significant hits are displayed in bold. *This gene also showed a genome-wide significant quadratic age effect. The most parsimonious model is listed in this table.

genome-wide significant associated loci. Supplementary Table S8 displays the top-10 genes for each phenotype and each age model.

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 (see Methods). We tested the associations of 9,975 gene sets derived from the MSigDB 7.0 (Subramanian et al., 2005) using gene-based p -values. Competitive testing was used and revealed five genome-wide significant gene sets (Table 3, see Supplementary Table S9 for top-10 gene sets and genes included). Two of these reached study-wide significance: the interleukin-1 (IL-1) receptor activity gene set for age-dependent genetic associations with cortical volume change and the response to interleukin-2 (IL-2) gene set for age-independent genetic associations with thalamic change. There were no overlapping genes in these gene sets. These gene sets are immune system-related, and both IL-1 and IL-2 are known to affect the growth and survival of neural cells (Hanisch and Quirion, 1996; Borsini et al., 2015). The finding of immune-related gene sets in both these structures is intriguing given the extensive reciprocal structural connections of thalamus with the cerebral cortex (Zhang et al., 2010; Bolkan et al., 2017) and the known phenotypic and genetic link between psychiatric and immune-related disorders (Lambert et al., 2013, Psychiatric Genomics Consortium, 2014; Wang et al., 2015; Jeppesen et al., 2019; Pouget et al., 2019).

Post-hoc analyses

Overlap with cross-sectional findings

SNP-based heritability estimates (h^2) of the rates of change based on linkage disequilibrium score regression (LDSC; Bulik-Sullivan et al., 2015) were small overall (Supplementary Table S10). For all phenotypes, the h^2 z-score was below 4, so we tested for genetic overlap with cross-sectional brain data and other phenotypes by applying approaches other than LDSC: 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, Materials and Methods). Supplementary Figure S6 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 S8 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, no overlap was seen for 11 of the measured phenotypes, and only up to 2 overlapping genes were observed for the remaining 4 phenotypes. These genes included *APOE*, a major genetic risk factor for AD (Wolfe et al., 2019), which influenced change in both amygdala and hippocampus differentially across the lifespan. Additional top genes for

Table 3: Gene-sets for age-(in)dependent effect on longitudinal brain changes.

Phenotype (change rate)	Age- dependency	GO-term	# genes ^a	P-value	Brief description
Cortex	linear	GO_SECRETORY_GRANULE_LOCALIZATION	11	6.39e-07	Any process in which a secretory granule is transported to, and/or maintained in, a specific location within the cell)
Cortex	linear	GO_INTERLEUKIN_1_RECEPTOR_ACTIVITY	6	6.80e-08	Combining with interleukin-1 to initiate a change in cell activity. Interleukin-1 is produced mainly by activated macrophages and is involved in the inflammatory response
Pallidum	constant	GO_FLAVONOID_GLUCURONIDATION	9	1.51e-06	The modification of a flavonoid by the conjugation of glucuronic acid. The resultant flavonoid glucuronosides are often much more water-soluble than the precursor.
Thalamus	constant	GO_RESPONSE_TO_INTERLEUKIN_2	12	1.12e-07	Any process that results in a change in state or activity of a cell or an organism (in terms of movement, secretion, enzyme production, gene expression, etc.) as a result of an interleukin-2 stimulus.
Thalamus	linear	GO_GTPASE_REGULATOR_ACTIVITY	259	2.63e-06	Modulates the rate of GTP hydrolysis by a GTPase.

Genome-wide significant gene sets based on gene ontology. Study-wide significant gene sets are displayed in bold. ^aSee Supplementary Table S9 for genes included in the gene set. Genes included in GO_INTERLEUKIN_1_RECEPTOR_ACTIVITY and GO_RESPONSE_TO_INTERLEUKIN_2 do not overlap.

volume change that had previously been identified in GWAS of cross-sectional volumes of the same structures were *KTN1* (kinectin 1 gene) for putamen (Hibar et al., 2015), *C16orf95* for ventricle volume (Elliot et al., 2018), and *APOC1* (Apolipoprotein C-1) for amygdala and hippocampus (Hibar 2017, Satizabal 2019). Extending this search to the top 200 (~1% of genes), we found no other overlapping genes above chance level. In the top 1,000 ranked genes (~5% of genes), overlapping genes did emerge (Supplementary Figure S6).

To test for global genomic overlap between our findings and GWAS of cross-sectional volumes we applied independent SNP-Effect Concordance Analyses (iSECA) (Nyholt, 2014; Materials and 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 3).

Overlap with other traits

We applied iSECA for overlap between our age-independent summary statistics for structural brain changes and several neuropsychiatric, neurological, physical, aging and disease-related phenotypes and psychological traits (Materials and Methods). We found significant genomic overlap ($p < 1.6\text{e-}04$) with genetic variants associated with depression (Howard et al., 2019), schizophrenia (Psychiatric Genomics Consortium, 2014), cognitive functioning (Savage et al., 2018), height (Yengo et al., 2018), body mass index (BMI; Yengo et al., 2018), and ever smoking (Watanabe et al., 2019). Despite significant pleiotropy between rates of change and these traits, the directions of effects varied across loci. (Figure 3, Supplementary Figure S7).

Of note, 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 3).

Gene expression in the brain across the lifespan

We determined mRNA expression for genome-wide significant genes and genes associated with genome-wide significant SNPs (Tables 1 and 2) in 54 tissue types and in both the developing and adult human brain, through GENE2FUNC (Watanabe et al., 2017). For the prioritized genes, a gene expression heatmap was created, based on GTEx v8 RNAseq data (GTEx Consortium, 2015). This revealed considerable expression levels across several brain tissues for the following genes: *ABR*, *TMEM30A*, *APOE*, *EPAS1*, *PLCD3*, and *DSCAM*, the latter showing higher relative expression in brain tissue compared to all other tissue types (Supplementary Figure S8A). *TMCO2* was predominantly expressed in the testis. Expression heatmaps based on BrainSpan data (Miller et al., 2014) revealed that *DACH1* shows highest relative expression during early prenatal stages (8-9 post conception weeks), compared to postnatal stages. A second cluster of genes demonstrated stable high relative expression levels throughout development

and across the lifespan (*APOE*, *ABR*, *TMEM30A*, *PID1*). Two additional genes, *EPAS1* and *PLCD3*, showed lower relative expression in the early prenatal stages and higher expression later in life (Supplementary Figure 8B).

Phenome-wide associations

For the prioritized SNPs and genes (Table 1 and 2), exploratory pheWAS (i.e., “phenome-wide”) analysis was performed to systematically analyze many phenotypes for association with the genotype and individual genes (Supplementary Table S11). PheWAS was performed using publically available data from the GWASAtlas (<https://atlas.ctglab.nl>; Watanabe et al., 2019). Both a single variant (rs72772740) and gene associations of *DACH1*, *GPR139* showed pleiotropic effects mainly in the metabolic domain, e.g., with estimated glomerular filtration rate and BMI (Supplementary Table S11, Supplementary Figure S9). *APOE* showed strong associations with cholesterol and lipids. Similarly, *TMCO2* and *PLCD3* showed significant associations with BMI-related phenotypes (Supplementary Table S11, Supplementary Figure S9).

Sensitivity analyses

We repeated the main analyses in various subgroups: 1) by adding four cohorts of non-European or mixed ancestry (N=540), 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=9,105, 3) by excluding diagnostic groups in each cohort leaving N=7,309, and 4) by including a covariate adjusting for disease status (Supplementary Tables S12-S14). In SNP-based analyses, effects sizes of SNPs were very similar in all subgroups, suggesting that our results are also applicable for individuals of non-European ancestry, the smaller cohorts, and in individuals irrespective of disease (Supplementary Table S12). For the gene-based analyses, a similar pattern was observed, with one notable exception: the *APOE* finding for hippocampus rate of change showing increasing influence of the top SNP with age, was no longer present when correcting for disease. This suggests that the *APOE* finding for hippocampus was driven by the presence of patients (Supplementary Table S13).

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, which did not change the findings (Supplementary Figure S7D).

Discussion

Here, we present the first GWAS investigating influences of common genetic variants on brain-structural changes in over 10,000 subjects. 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 discovered novel

genetic effects that influence inter-individual differences in both development and aging of brain structures. Many of the genes implicated play a crucial role in early, prenatal brain development. We identified these genes in a population aged 4 to 99, suggesting that the same genetic variants are also crucial for brain-structural changes later in life.

Our findings show genomic overlap with psychiatric and physiological phenotypes that are associated with longitudinal brain-structural changes such as schizophrenia, smoking, cognitive functioning, and body mass index (Hulshoff Pol and Kahn, 2008; Bobb et al., 2014; Schnack et al., 2015; Kim et al., 2018). Additionally, we find the *APOE* gene, a major risk factor for AD (Wolfe et al., 2019), to influence amygdala and hippocampus rates of change with varying effects across the lifespan, with probably most pronounced effects in those affected with brain disorders. Gene-set findings imply a role for immune-related processes. Several of the identified genetic variants and genes were linked to metabolic phenotypes, and we found genetic overlap with body mass index, suggesting a role for metabolic processes in longitudinal brain changes.

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 (Fjell et al., 2015; Walhovd et al., 2016), whereas the age-dependent effects can be interpreted as possible changing effects of genes or gene expression during life (Kang et al., 2011). The genome-wide meta-regression approach employed here may enable future GWAS for other phenotypes that change over the human lifespan.

How exactly variation in these genes impacts brain changes in health and disease cannot be answered based on genome-wide association studies. In this, our findings may direct future studies into brain development and aging, and prevention and treatment of brain disorders. For neurodegenerative disorders, for example, identifying genetic variants that influence brain atrophy over time might well be equally or more important than the 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.

Materials and Methods

Ethical approval and data availability

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*). 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>.

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 10,163 subjects aged 4 to 99 (50% female, 22% patients). Please see Supplementary Figure S1 and Supplementary Table S1 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 (Fischl et al., 2002, 2004; Reuter, Schmansky, Rosas, & Fischl, 2012; see Supplementary Table S2 for details per cohort). We chose these measures based on the fact that they show generally high test-retest reliability for cross-sectional measures e.g. (Iskan et al., 2015; Liem et al., 2015; Wonderlick 2009), 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 this analysis: while this is common practice for investigating cross-sectional brain volumes (Voevodskaya et al., 2014), the influence of overall head size on brain changes over time is small (Supplementary Figure S2). 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 (LOWESS; Cleveland, 1979) implemented in R (R Core Team, 2018). 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 dataset (1000 Genomes Project Consortium, 2015) through the Michigan imputation server (<https://imputationserver.sph.umich.edu/> - Das et al., 2016) or the Sanger imputation server (McCarthy et al., 2016) (Supplementary Table S3). 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 population (International HapMap Consortium, 2010). 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). 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* (Feng et al., 2014) for analysis (Supplementary Table S3). 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-analyze their data, which usually involved removal of outliers in the phenotypic data.

Meta-analysis and Meta-regression

In the cohorts of European ancestry (N=9,604) we tested three models aggregating the cohort-level data for each phenotype, using standard-error weighted meta-analysis or meta-regression: Under the assumption that effect sizes of single nucleotide polymorphisms (SNPs) were consistent across the lifespan, where the subscript C denotes a cohort and ε an error term.

- 1) Effect_SNP_C ~ b₀ + ε_C , under the null hypothesis that b₀ = 0.

Given that brain changes throughout life are dependent on age, the effects of a genetic variant on brain change is 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 (Supplementary Table 1 and Supplementary Figure S1), it was possible to

calculate the age-dependent effects across the life span 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) (Baker et al., 2009). We estimated the following model under the assumption that the effects of SNPs may vary in size or direction across the lifespan:

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

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

SNP data were aligned using METAL (Willer, Li, & Abecasis, 2010) for all three analyses. The age-independent effect of SNPs (model 1) was computed in METAL. For the age-dependent analyses the aligned data were imported into R (version 3.5.0, R Core Team, 2018) and fixed effects meta-regression was performed using the R-package metafor (version 2.0-0, Viechtbauer, 2010). 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 results (Watanabe, Taskesen, Van Bochoven, & Posthuma, 2017). 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 v7 (Lonsdale et al., 2013)), blood eQTL browser (Westra et al., 2013), BIOS QTL browser (Zhernakova et al., 2017), BRAINEAC (Ramasamy et al., 2014), MuTHER (Grundberg et al., 2012), xQTLServer (Ng et al., 2017), the CommonMind Consortium (Fromer et al., 2016) and 3D chromatin interactions from HI-C experiments of 21 tissues/cell types (Schmitt et al., 2016). 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 $p + q = 1$, $f(x) = p \cdot (h(x) + g(x)) + q \cdot h(x) = h(x) + p \cdot g(x)$. We created a rate of change curve for non-carriers as $f(x) - p \cdot g(x)$ and a rate of change curve of carriers as $f(x) + q \cdot g(x)$. 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 MAGMA (version 1.07b; de Leeuw et al., 2015) 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 ENSG v92 (Zerbino et al., 2018) as is used in the FUMA pipeline (Watanabe et al., 2017). 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 (defined using NCBI 37.3 gene definitions) was used as the test statistic. LD correction was based on estimates from the 1000 Genomes Project Phase 3 European ancestry samples (1000 Genomes Project Consortium, 2015). 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 analyze sets of genes in order to test for association of genes belonging to specific biological pathways or processes. MAGMA applies a competitive test to analyze 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 sets (Gene Ontology Consortium, 2015) curated from MsigDB 7.0 (Subramanian et al., 2005).

Multiple testing corrections

We investigated annual rates of change for 15 brain phenotypes, but these are correlated to some extent (Supplementary Figure S2). We therefore estimated the effective number of independent variables based on matrix

spectral decomposition (Nyholt, 2004) for the largest adolescent cohort (IMAGEN; N=1,068) and for the largest elderly cohort (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 the fact that we performed 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 $0.05/18,217 = 2.64e-06$, and a study wide significance of $2.64e-06/(13.93*3)$, i.e. $p < 6.6e-08$. 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. $p < 1.20e-07$.

Post-hoc analyses

SNP heritability

SNP heritabilities, h^2_{SNP} , were estimated by using linkage disequilibrium (LD) score regression (LDSR; Bulik-Sullivan et al., 2015) 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 Project (1000 Genomes Project Consortium, 2015) restricted to HapMap3 SNPs (International HapMap Consortium, 2010). 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 higher (Bulik-Sullivan et al., 2015).

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 from (Elliott et al., 2018; Hibar et al., 2017; Satizabal et al., 2019; Grasby et al., 2020) were requested/downloaded from (<http://enigma.ini.usc.edu/research/download-enigma-gwas-results/>; 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 correction (Benjamini and Hochberg, 1995) was applied to determine over- or under-representation of genes from our longitudinal GWAS to the cross-sectional previously published GWAS.

Genetic overlap with cross-sectional results and other traits

To investigate genetic overlap with other traits across the genome we applied an adapted version of iSECA (independent SNP effect concordance analysis; Nyholt, 2014) 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 are generated containing binomial tests for pleiotropy and Fisher's exact tests for concordance. An empirical p -value for overall pleiotropy and concordance is 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 aggression (Pappa et al., 2016), alcohol dependence (Walters et al., 2018), Alzheimer's disease (Lambert et al., 2013), attention-deficit/hyperactivity disorder (Demontis et al., 2019), autism (Psychiatric Genomics Consortium, 2017), bipolar disorder (Stahl et al., 2019), body mass index (Yengo et al., 2018), brain age gap (Kauffman et al., 2019), cognitive functioning (Savage et al., 2018), depression (Howard et al., 2019), diabetes type 2 (Scott et al., 2017), ever smoking (Watanabe et al., 2019), focal epilepsy (The International League Against Epilepsy Consortium on Complex Epilepsies, 2018), height (Yengo et al., 2018), inflammatory bowel disease (Liu et al., 2015), insomnia (Jansen et al., 2019), multiple sclerosis (Sawcer et al., 2011), Parkinson's disease (Nalls et al., 2018), rheumatoid arthritis (Okada et al., 2014) and schizophrenia (Psychiatric Genomics Consortium, 2014). These phenotypes were chosen because of known associations with brain structure or function, and availability of summary statistics based on large GWA-studies.

Apart from these, we also 1) included intracranial volume (Adams et al., 2016) 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 $0.05/15 \times 22$ (#change rates * #phenotypes tested) = $1.6e-04$.

Brain gene expression

GENE2FUNC, a core process of FUMA (Functional Mapping and Annotation of Genome-wide Association Studies; <http://fuma.ctglab.nl>; Watanabe et al.,

2017), was employed to analyze gene expression patterns. For this, a set of 16 genes was used as input, including all genome-wide significant genes and genes harboring genome-wide significant SNPs (compare Table 1 and 2). Gene expression heatmap was constructed employing GTEx v8 (GTEx Consortium, 2015; 54 tissue types) and BrainSpan RNA-seq data across 29 different ages or 11 different developmental stages (Miller et al., 2014). 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 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 GWASAtlas (<https://atlas.ctglab.nl>; Watanabe et al., 2019). 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, resulting in a Bonferroni corrected p -value threshold of $1.05\text{e-}05/19$, i.e., $p < 5.53\text{e-}07$.

Sensitivity analyses

The main analyses include available data from all cohorts with European ancestry (N=9,623). The four cohorts of non-European and mixed ancestry together consist of 540 subjects, who are predominantly children and adolescents (Supplementary Table S3). 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=10,163). In a second analysis, we excluded the 9 cohorts that had $N < 75$ or mean scanning interval < 0.5 years (Supplementary Table S2), leaving N=9,105 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=7,309) and by correcting for disease status.

Figure legends

Figure 1: Phenotypic brain changes throughout the lifespan.

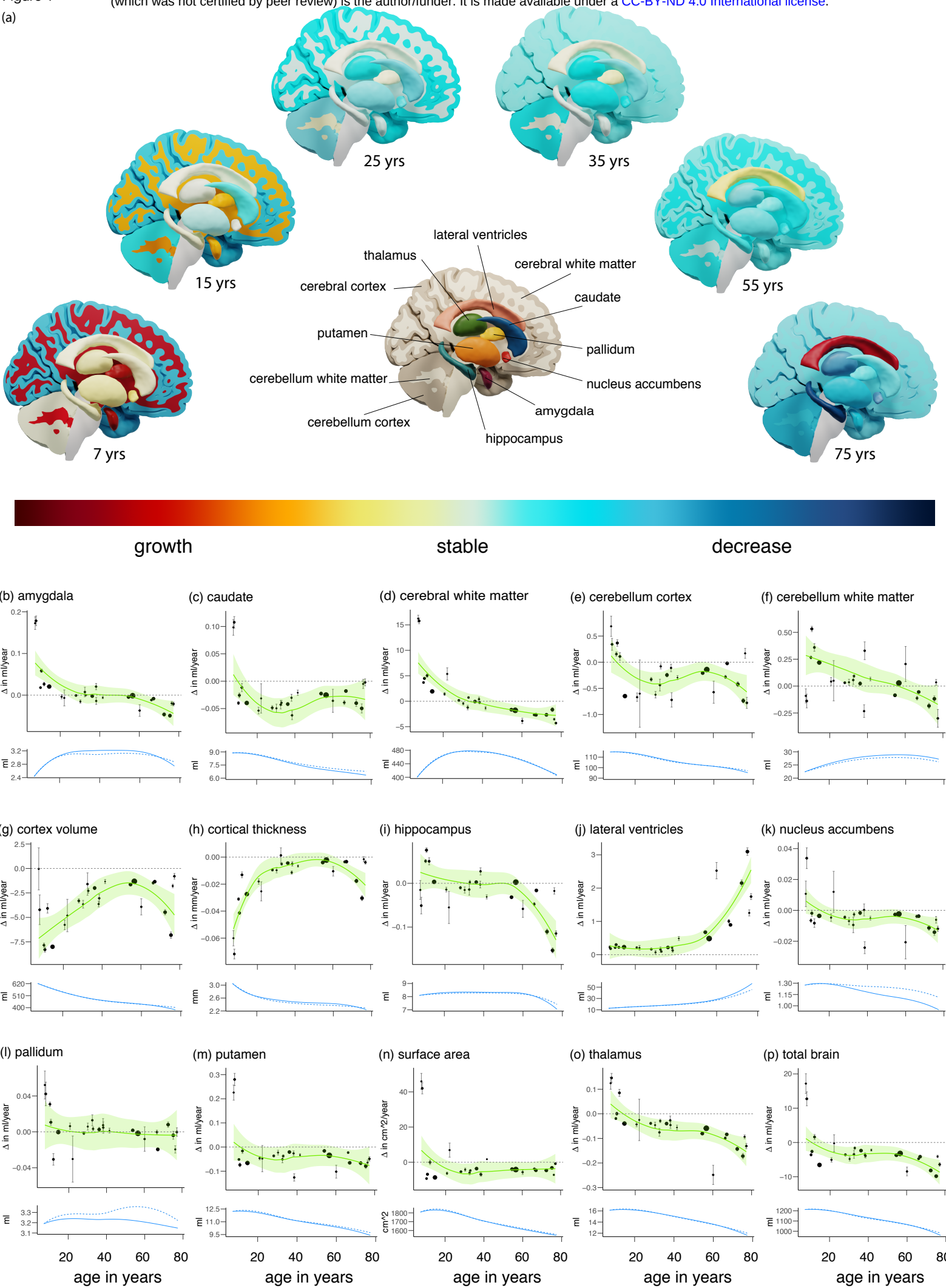
Visualization of growth and decline of brain structures throughout the lifespan. The subcortical structures are shown in exploded view (a). Individual change rates are shown for (b) amygdala, (c) caudate, (d) cerebral white matter volume, (e) cerebellum cortex volume, (f) cerebellum white matter volume, (g) cortex volume, (h) cortical thickness, (i) hippocampus, (j) lateral ventricle volume, (k) nucleus accumbens, (l) pallidum, (m) putamen, (n) surface area, (o) thalamus and (p) total brain. Annual rates of change Δ per cohort. “For each structure, the estimated trajectories with confidence intervals (*in green*) are displayed in the top row (b-p). The size of the points represents the relative size of the cohorts. Standard errors are displayed in gray. Means and standard deviations are based on raw data – no covariates were included. 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*).

Figure 2: **Genetic effects on rates of brain changes throughout the lifespan.** a) genome-wide significant SNPs and genes with effects on brain changes at their respective loci across the human genome; Illustrations of the two significant genome-wide loci with significant associated genes for b) age-independent effect of *GPR139* and rs72772740 on lateral ventricle change and c) age-dependent effect of *DACH1* and rs573983368 on white matter change; both b) and c) are represented by Manhattan plot, locus plot, meta-regression plot with the meta-regression curve with 95% confidence interval in red and effect size of cohorts represented by circle size, and trajectory plot with the estimated trajectories of the volumes themselves for carriers and non-carriers of the top SNP; Illustrations of the three other genome-wide genetic effects with d) age-dependent effect of top SNP of *APOE* on amygdala change and e) age-dependent effect of the top SNP of *APOE* on hippocampus change; d) and e) are represented by meta-regression curve and estimated trajectories for carriers and non-carriers of the effect allele.

Figure 3: 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 left of color legend). P -values for pleiotropy between change rates of structural brain measures and head size (total brain volume) and the cross-sectional brain measure are displayed on the right (columns right of color legend). Significant overlap ($p < 1.6e-04$) is marked with *.

Figure 1
(a)



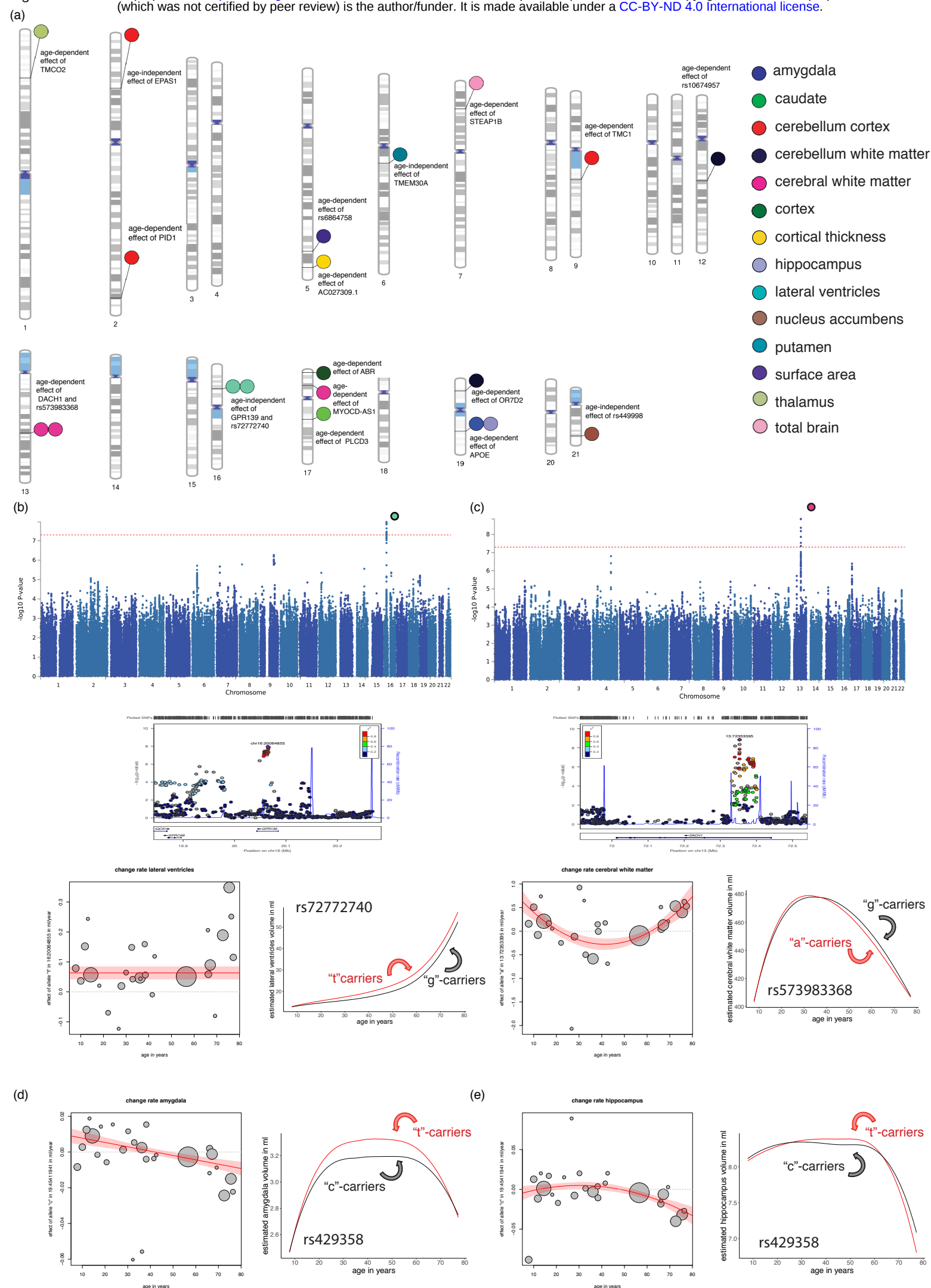
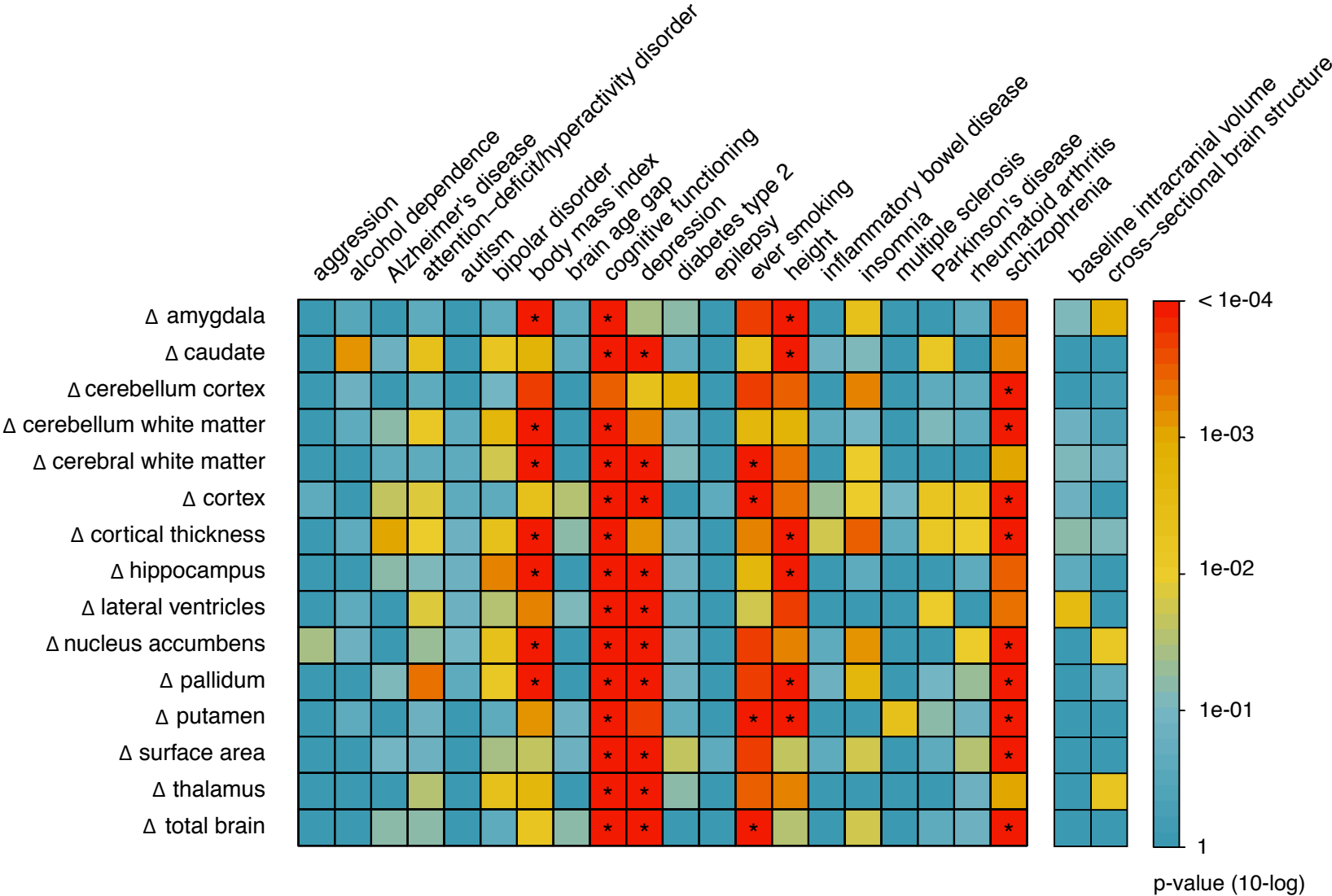


Figure 3



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Conflicts of interest

BF has received speaking fees from MEDICE Arzneimittel Pütter GmbH & Co. BWJHP has received research funding from Jansen Research and Boehringer Ingelheim. CA has been a consultant to or has received honoraria or grants from Acadia, Angelini, Gedeon Richter, Janssen Cilag, Lundbeck, Minerva, Otsuka, Roche, Sage, Servier, Shire, Schering Plough, Sumitomo Dainippon Pharma, Sunovion and Takeda. CDW is an employee of Biogen Inc. DJS has received research grants and/or consultancy honoraria from Lundbeck and Sun. GJB receives honoraria for teaching from GE Healthcare. HB is on the Advisory Board Nutricia Australia. HEH has received travel fees for membership of the Steering Committee of the Lundbeck Foundation Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research and for two presentations from Philips. These concerned activities unrelated to the submitted work. HJG has received travel grants and speaker's honoraria from Fresenius Medical Care, Neuraxpharm, Servier and Janssen Cilag as well as research funding from Fresenius Medical Care. LP has served as an advisor or consultant to Shire, Takeda and Roche. She has received speaking fees from Shire and Infectopharm. The present work is unrelated to these relationships. MHJ received grant support from the Brain and behavior Foundation (NARSAD) Independent Investigator grant number 20244. MMN has received fees for memberships in Scientific Advisory Boards from the Lundbeck Foundation and the Robert-Bosch-Stiftung, and for membership in the Medical-Scientific Editorial Office of the Deutsches Ärzteblatt. MMN was reimbursed travel expenses for a conference participation by Shire Deutschland GmbH. MMN receives salary payments from Life & Brain GmbH and holds shares in Life & Brain GmbH. All these concerned activities outside the submitted work. NJ and PMT are MPI's of a research grant from Biogen, Inc (Boston, USA) for work unrelated to

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