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Genomic studies across the lifespan point to early mechanisms determining subcortical volumes

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Disclosures

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Abstract

Background: Subcortical brain structures play a key role in pathological processes of age-related neurodegenerative disorders. Mounting evidence also suggests that early-life factors may have an impact on the development of common late-life neurological diseases, including genetic factors that can influence both brain maturation and neurodegeneration.

Methods: Using large population-based brain imaging datasets across the lifespan (N≤40,628) we aimed to: (i) estimate the heritability of subcortical volumes in young (18–35), middle (35–65), and older age (65+), and their genetic correlation across age groups; (ii) identify whether genetic loci associated with subcortical volumes in older persons also show associations in early adulthood, and explore underlying genes using transcriptome-wide association studies; (iii) explore their association with neurological phenotypes.

Results: Heritability of subcortical volumes consistently decreased with increasing age. Genetic risk scores for smaller caudate nucleus, putamen and hippocampus volume in older adults were associated with smaller volumes in young adults. Individually, ten loci associated with subcortical volumes in older adults also showed associations in young adults. Within these loci, transcriptome-wide association studies showed that expression of several genes in brain tissues (especially *MYLK2* and *TUFM*) was associated with subcortical volumes in both age-groups. One risk variant for smaller caudate nucleus volume (*TUFM* locus) was associated with lower cognitive performance. Genetically-predicted Alzheimer's disease was associated with smaller subcortical volumes in middle and older age.

Conclusions: Our findings provide novel insights into the genetic determinants of subcortical volumes across the lifespan. More studies are needed to decipher the underlying biology and clinical impact.

Keywords

Genomics; Epidemiology; Lifecourse approach; Subcortical volumes; Dementia

Introduction

Subcortical structures (hippocampus, caudate nucleus, putamen, pallidum, accumbens, amygdala and thalamus) are involved in many neural processes, from autonomic and sensorimotor functions to memory, decision making and processing of reward and threat signals (1–5). These structures also play a key role in pathological processes of age-related neurodegenerative disorders, including Parkinson disease (PD) and Alzheimer's disease (AD). Volumes of subcortical structures can be measured quantitatively in large population-based samples using brain Magnetic Resonance Imaging (MRI) and were shown to decrease with ageing and neurodegenerative diseases (6–15).

Mounting evidence suggests that factors already present at an early age may have an impact on the development of late-life neurological diseases, likely due to a complex combination of genetic and environmental factors that influence both brain maturation and neurodegeneration (16,17). Identifying early-life determinants of neurological diseases occurring in older age could therefore be crucial for developing more efficient prevention strategies. MRI-based measures of subcortical brain structures represent a powerful intermediate phenotype to decipher these early determinants, as they show alterations many years before the onset of clinical symptoms (18).

Recently, genome-wide association studies (GWAS) have enable substantial progress in deciphering genes underlying variations in volumes of brain structures, identifying 38 independent genetic risk loci for subcortical volumes (15,19–21). To date, most of these studies have focused on middle-aged and older adults. A recent study found that AD genetic risk variants were associated with smaller hippocampal volume in young adults, suggesting that genetic determinants of late-life neurodegenerative diseases may already be associated with subtle variations in brain structure early in life (22). However, genetic determinants of MRI-based measures may also change over time, either because of different underlying physiological or pathological processes between young and older persons or because of time-varying exposures to environmental risk factors across the lifespan (16,23,24).

Exploring the shared genetic variation underpinning early and late structural brain variations, specifically of subcortical brain volumes, could provide important novel insight into the time-course of structural brain changes throughout the adult lifespan and into the mechanisms underlying brain aging and their connection with factors modulating brain maturation. This could contribute to exploring early biological processes driving late-onset neurodegenerative diseases and open new avenues for preventive approaches.

Using large population-based brain imaging datasets across the adult lifespan we aimed to: (i) estimate the heritability of subcortical volumes from young adulthood to older age, and assess the amount of shared genetic variation across age groups; (ii) identify whether genetic loci associated with subcortical volumes in older age also show association with subcortical volumes in early adulthood, and explore underlying genes using transcriptome-wide association studies; (iii) explore the clinical significance of these results in relation with cognition, AD, and PD.

Methods and Materials

Study Population

Analyses were conducted in three age groups: young (18–35), middle-aged (35–65), and older adults (65+). The 35-years cut-off (also corresponding to the upper-age limit of i-Share participants) was based on previous neuroimaging studies indicating that some brain structures, including subcortical structures, reach a peak volume around this age (6,25). The 65-years cut-off (also the lower-age limit for the 3C-Dijon participants) corresponds to an age after which aging features on brain imaging tend to accelerate more steeply (6,25).

Heritability analyses

Heritability analyses were conducted on individual level data from three cohorts:

Population-based cohort studies of unrelated individuals

The Internet-based Students HeAlth Research Enterprise (i-Share) study is an ongoing prospective population-based cohort study of French-speaking students (26). 1,777 participants aged 18–35 years had both brain MRI and genome-wide genotypes (Supplementary Methods).

The Three-City Dijon (3C-Dijon) Study is a population-based cohort study (27). 1,440 participants aged 65 years and older had both brain MRI and genome-wide genotypes, excluding participants with dementia, stroke history, or brain tumors at baseline (Supplementary Methods).

Family-based cohort studies

The Framingham Heart Study (FHS) is a community-based cohort study comprising three generations of participants. 1,999 participants aged 36–64 years and 1,828 participants aged 65 years and older had both brain MRI and genome-wide genotypes, excluding participants with stroke history or other neurologic disorders confounding the assessment of brain volumes at time of MRI (Supplementary Methods).

Analyses of shared genetic variation across the lifespan

To analyze genetic associations with subcortical volumes in young adults we used the aforementioned 1,777 i-Share participants with high quality brain MRI and genome-wide genotype data. To derive genome-wide significant associations with subcortical structures in middle-aged to older adults we used summary statistics of the largest published meta-analyses of subcortical volumes GWAS (detailed in Supplementary Methods) for optimal power (15,20). In secondary analyses we also used smaller meta-analyses without a subset of cohorts comprising younger age groups leading to a sample size of 19,555 participants (detailed in Supplementary Methods). For hippocampal volume we used a previously published GWAS meta-analysis (21). Participants with prevalent dementia, stroke or other neurological pathologies potentially influencing brain measurements at the time of MRI were excluded in all but one meta-analyses (20).

This study was approved by the ethics committees of participating studies, and written informed consent was obtained from all participants.

MRI Acquisition and Phenotyping

MRI acquisition parameters and phenotyping methods in individual cohorts are presented in the Supplementary Methods and have been described in detail (15,20,21,28).

We defined subcortical volumes by the total (left+right) grey matter volumes (cm^3) of the accumbens, amygdala, caudate nucleus, hippocampus, pallidum, putamen, and thalamus. The accumbens volume was not available in the 3C-Dijon study.

Genotyping, quality control, and imputation

Genome-wide genotyping platforms, quality control and imputation procedures are described in the Supplementary Methods.

Statistical analyses

Analyses performed in this study are summarized in Figure 1.

Heritability analyses

Heritability analyses were adjusted for age, sex, total intracranial volume, and the first four principal components of population stratification.

Population-based cohort studies of unrelated individuals

To estimate heritability for each subcortical volume in i-Share and 3C-Dijon, we used GCTA (v1.26.0) to estimate the proportion of phenotype variance explained by genome-wide single nucleotide polymorphisms (SNPs) (Figure 1, Supplementary Methods) (29).

Family-based cohort studies

To estimate heritability for subcortical volumes in FHS, we used the variance component model implemented in SOLAR accounting for familial relationships to determine the ratio of the genetic variance to the phenotypic variance (30). Mixed models were fit including fixed effects for covariates and additive effects for additive polygenetic and residual error terms.

Genetic correlation analyses

We used LD Score Regression (LDSR) to estimate the genetic correlation between subcortical volumes in young and older adults (Figure 1) (31,32). For the older population, we first used the latest, largest published GWAS meta-analysis of subcortical brain volumes (15,20). To confirm that the effects were not driven by the youngest individuals in the GWAS meta-analyses, we conducted secondary analyses using subcortical brain volumes GWAS meta-analyses without cohorts or consortia comprising younger participants (as described for analyses of shared genetic variation across the lifespan). For young adults, we performed GWAS of subcortical volumes in i-Share, adjusting for age, sex, total intracranial volume, and the first four principal components of population stratification. We used a linear

mixed model implemented in GCTA-MLMA-LOCO (33). We used a method implemented in R (matSPDlite) to correct for multiple testing (34). Among the seven subcortical volumes studied, the number of independent tests was estimated at 4.0 based on the correlation matrix between all phenotypes, leading to a Bonferroni corrected significance threshold of $p<1.25\times10^{-2}$.

Single variant analyses and Genetic Risk Score approaches

First, we selected published genome-wide significant associations in middle-aged to older adults (15,20) and looked up associations with the corresponding phenotype in young adults (i-Share), for the lead SNP and nearby variants (±250 kb) in moderate to high linkage disequilibrium (LD) (LD-r^2>0.5). To define significance thresholds we corrected for the four independent phenotypes in i-Share and the number of independent loci tested for each subcortical volume: accumbens: $p<3.13\times10^{-3}$; amygdala: $p<1.25\times10^{-2}$; caudate: $p<1.25\times10^{-3}$; hippocampus: $p<2.08\times10^{-3}$; pallidum: $p<2.08\times10^{-3}$; putamen: $p<1.39\times10^{-3}$; thalamus: $p<6.25\times10^{-3}$.

Second, we generated genetic risk scores (GRS) for lower subcortical volumes in young adults (i-Share) by summing the number of published genome-wide significant independent risk alleles identified from subcortical volume GWAS in middle-aged to older adults, weighting each risk allele by the regression coefficient for the corresponding SNP in the published GWAS (Supplementary Methods). Associations were tested using linear regression models in R v3.6.1 and adjusted for age, sex, total intracranial volume, and the first four principal components of population stratification. To account for multiple testing, we corrected for four independent phenotypes ($p<1.25\times10^{-2}$). As a sensitivity analysis, GRS analyses were repeated using summary statistics of the subcortical volumes GWAS conducted after removing cohorts with young participants as described above (Figure 1).

Transcriptome-wide association study

To explore genes underlying genetic associations with subcortical volumes across the lifespan we performed transcriptome-wide association studies (TWAS) using TWAS-Fusion (Figure 1, Supplementary Methods) (35). We used summary statistics from the aforementioned published GWAS meta-analyses of subcortical volumes (15,20) and 17 publicly available gene expression quantitative trait loci (eQTL) reference panels from blood, brain and peripheral nerve tissues (Supplementary Methods). We used TWAS-Fusion to estimate the TWAS association statistics between predicted expression and each subcortical volume (35). Transcriptome-wide significant genes were determined in each tissue expression panel after correcting for the average number of features (3793.5 genes) and 4 independent phenotypes ($p<3.30\times10^{-6}$). Transcriptome-wide significant genes were then tested in conditional analysis (TWAS-Fusion) (35). Next, to ensure that observed associations did not reflect random correlation between gene expression and non-causal variants associated with subcortical volumes, we performed a colocalization analysis (COLOC) on the conditionally significant genes ($p<0.05$) to estimate the posterior probability of a shared causal variant between the gene expression and trait association (PP4) (36). Genes presenting a PP4≥0.75, for which eQTLs did not reach genome-wide significance in association with subcortical volumes, and were not in LD ($r^2<0.01$) with a

lead SNP of genome-wide significant risk loci for subcortical volumes, were considered as novel.

In order to test colocalized associations in a younger population, we used the individual-level prediction of the gene expression option implemented in the Fusion software to generate expression-weights in i-Share (Supplementary Methods). The significance threshold accounted for the number of genes colocalized in ≥1 tissue for each phenotype (accumbens: $p<0.05$; amygdala: $p<0.05$; caudate: $p<2.17\times10^{-3}$; hippocampus: $p<1.67\times10^{-2}$; pallidum: $p<2.94\times10^{-3}$; putamen: $p<3.85\times10^{-3}$; thalamus: $p<0.05$).

Lifetime brain gene expression profile

We examined the spatio-temporal expression pattern of genes in loci reaching genome-wide significance in the subcortical volumes GWAS, TWAS-COLOC significance and at least nominal significance in the i-Share TWAS. We used a public database (https://hbatlas.org/) comprising genome-wide exon-level transcriptome data from 1,340 tissue samples from 16 brain regions of 57 postmortem human brains, from embryonic development to late adulthood (37).

Clinical correlates

First, we explored the relation of loci associated with subcortical volumes in young and older populations or at least nominally significant in TWAS in i-Share (Table 1) with AD, PD, and general cognitive function using summary statistics of the latest, largest published GWAS (38–40). Accounting for 10 independent loci ($r^2<0.5$) and three traits, the significance threshold was $p<1.67\times10^{-3}$.

Second, we tested whether genetically predicted AD or PD have an impact on subcortical volumes in the general population in young, middle-aged and older adults using the generalised summary data-based Mendelian randomization (GSMR) tool implemented in GCTA (Supplementary Methods) (29,41). The significance threshold accounted for four independent subcortical volumes and two diseases ($p<6.25\times10^{-3}$).

Data availability

Data supporting these results can be made available upon reasonable request from the corresponding author.

Results

Heritability and genetic correlation of subcortical volumes across the lifespan

SNP-heritability estimates for all subcortical volumes in young, middle-aged, and older adults are presented in Figure 2 and Table S1. We observed a decreasing trend of the average SNP-heritability estimates of subcortical volumes in cohorts of increasing age (Figure 2 – Panel A), and a similar decreasing trend for most individual subcortical volumes (Figure 2 – Panel B), both in unrelated and family-based population-based studies.

Most subcortical volumes were genetically correlated with each other among middle-aged to older adults, while in young adults genetic correlations reached significance after correction for multiple testing between hippocampus and amygdala, pallidum and caudate nucleus, and putamen and pallidum. Genetic correlations between young and middle-aged to older adults for the same individual subcortical volumes were significant for the caudate nucleus and the pallidum (Figure 3). These results were similar when using the published GWAS meta-analyses of subcortical volumes in middle-aged to older adults (Figure 3 – Panel A), and the secondary GWAS meta-analyses in older adults (Figure 3 – Panel B).

Genetic associations with subcortical volumes across the lifespan

Out of the 38 genome-wide significant loci for subcortical volumes in middle-aged to older adults, 10 were significantly associated with the same volume, in the same direction, in young adults (Table 1, Table S2): four in the caudate nucleus, two in the hippocampus and the putamen respectively, and one in the amygdala and the pallidum. The most significant association in young adults was for rs8017172 ($p=1.43\times10^{-7}$), near *KTN1*, with putamen volume.

GRSs for smaller subcortical volumes derived from GWAS in middle-aged to older adults were significantly associated with smaller volumes of the same structure in young adults for putamen, caudate nucleus, hippocampus, amygdala, and pallidum (Table 2). The most significant association was observed for the putamen ($p=5.04\times10^{-11}$). When deriving the GRS from the secondary meta-analyses of GWAS in older adults exclusively, associations remained significant for the putamen, caudate nucleus, and hippocampus.

We then sought to explore putative causal genes underlying genome-wide significant associations with subcortical volumes using TWAS, initially based on published GWAS meta-analyses in middle-aged and older adults (Figure 1). Among all genes showing transcriptome-wide significant associations, 54 presented a high colocalization posterior probability of sharing a causal variant between the gene expression and trait association (COLOC PP4≥0.75) with at least one subcortical volume, mostly in brain tissues (Figure S1, Table S3): 23 with caudate nucleus, 17 with pallidum, 13 with putamen, three with hippocampus, and one respectively with nucleus accumbens, amygdala, and thalamus. Among these 54 genes, 30 were in loci that did not reach genome-wide significance in the subcortical volumes GWAS and can be considered as novel (Table S3). Although we lacked power to detect transcriptome-wide associations in i-Share, we detected significant signals after multiple testing correction for 4 of the 54 colocalized genes described above, all at the genome-wide significant subcortical volume GWAS locus chr20q11.21 (Figure 4, Figure S1, Table S3): lower expression of *MYLK2* in putamen was associated with smaller caudate nucleus and putamen volume, higher expression of *FRG1B*, *MLLT10P1* and *RP4-610C12.4* in basal ganglia and cerebellum with smaller pallidum volume. With an exploratory purpose, we also considered 13 additional genes showing nominally significant associations in the young adult TWAS (Figure 4), including: 7 genes/transcripts for caudate nucleus (at chr16p11.2-12.1: *CCDC101*, *NPIPB7*, *NPIPB9*, *TUFM*, *EIF3C*, *RP11-1348G14.4*, *RP11-22P6.2*), 2 for pallidum (at chr20p11.21: *ENTPD6*, *PYGB*), and 4 for putamen (at chr5q14.3: *CTC–498M16.4*, *TMEM161B*, *TMEM161B–AS1*; and

chr20q11.21: *MLLT10P1*). Of note, the chr16p11.2-12.1 locus also showed significant association with the caudate nucleus in young adults (Table 1 and Table S2). Most TWAS-COLOC genes from genome-wide significant risk loci for subcortical volumes that also showed nominally significant TWAS association in young adults were described to have constant expression levels in subcortical regions throughout the life course, including in the prenatal period (Figure S2).

Clinical correlates

When exploring the association of the 14 genetic variants (in 10 independent loci) associated with subcortical volumes in both young and older adults (Table 1) with AD, PD, and general cognitive function we observed a genome-wide significant association of the lead SNP for smaller caudate nucleus volume at chr16p11.2-12.1 with lower general cognitive function (Table 3). No association reached significance with AD and PD after multiple testing correction.

Using GSMR, genetically predicted AD was significantly associated with smaller volumes of most subcortical structures except pallidum in dementia-free middle-aged and older adults from the general population, and with larger putamen volume in young adults (Figure 5, Table S4). Genetically predicted PD was significantly associated with larger thalamus volume in young adults (Figure 5, Table S4).

Discussion

In large population-based cohort studies across the adult lifespan, we identified a consistent trend towards decreasing heritability of subcortical volumes with increasing age. We observed significant genetic correlation of caudate nucleus and pallidum volumes between young and older adults. GRSs for smaller caudate nucleus, putamen or hippocampus volumes in older adults were significantly associated with smaller volumes of the same structures in young adults. Individually, ten of 38 independent loci associated with subcortical volumes in older adults also showed significant associations with the corresponding volumes in young adults. Using TWAS with colocalization analyses, we found evidence for expression levels of 16 genes to be significantly associated with caudate nucleus, putamen, or pallidum volume both in older and young adults, pointing to biological pathways underlying structural brain changes across the adult lifespan. One genome-wide significant caudate nucleus locus in older and young adults (at *TUFM*) was associated with lower general cognitive function at genome-wide significance. We also observed an association of genetically determined AD with smaller volumes of most subcortical structures in middle-aged and older dementia-free adults.

The observed heritability trends of subcortical volumes across the adult lifespan, both in an unrelated and family-based population-based setting, support and expand on a previous meta-analysis of brain volume heritability estimates in twin and family studies. The latter showed increasing heritability from childhood to early adulthood and decreasing heritability from young adulthood to old age (42). Potential explanations include an increase of the environmental contribution to variation in subcortical volumes with increasing age, thus

leading to a relative decrease of the genetic contribution, differential timing of gene expression during life, or age of onset of some disorders (43).

Genetic variants associated with smaller subcortical volumes in older persons were associated with smaller volumes of the same structure already in early adulthood, both individually and aggregated in a GRS. These results suggest that biological pathways influencing subcortical volumes in older age already have an impact on the latter in young adulthood. Although our analyses only focused on adult age, one could speculate that at least some of the susceptibility variants for smaller subcortical structures already showing significant associations at age 20 may be involved in developmental processes. This is supported by a recent study showing that polygenic risk scores for subcortical volumes in middle-aged to older adults were already associated with these volumes during infancy and early childhood (44). Several genes in loci associated with subcortical volumes in older persons were reported to be involved in neurodevelopmental processes in experimental work and are implicated in Mendelian disorders (15). *FAT3* at the chr11q14.3 locus that also showed association with caudate nucleus volume in i-Share, was for instance shown to be involved in neuronal morphogenesis and cell migration (15).

Ten individual loci associated with smaller subcortical volumes in older adults were already associated with smaller volumes of the same structures in young adults. We also showed association of subcortical volumes with up- or down-regulation of three genes in loci associated with caudate nucleus, putamen and pallidum volumes both in older and young adults: *MYLK2*, *FRG1B* and *MLLT10P1*. Among these, upregulation of *MYLK2* expression in brain tissues was significantly associated with larger caudate nucleus and putamen volume, in both older and young adults (Figure 4, Figure S3). In brain single-cell RNA sequencing analyses in mice, *mylk2* appears to be expressed in arterial and arteriolar smooth muscle cells and in pericytes (45,46). *MYLK2* encodes a myosin light chain kinase, a calcium/calmodulin dependent enzyme, harboring rare mutations causing hypertrophic cardiomyopathy (47).

Expression levels of four genes (*CCDC101*, *NPIPB7*, *NPIPB9* and *TUFM*) in a caudate nucleus GWAS locus that also shows significant association in young adults (chr16p11.2-12.1, Table 1) were associated with caudate nucleus volume at transcriptome-wide significance in older adults and nominal significance in young adults. Among these, increased *TUFM* expression was associated with smaller caudate nucleus volume, with evidence for colocalization in several tissues (Figure 4, Figure S3). *TUFM* is involved in combined oxidative phosphorylation deficiency 4 (COXPD4), a disease causing developmental regression, microcephaly and basal ganglia atrophy (48,49). Interestingly, the lead variant associated with smaller caudate nucleus at chr16p11.2-12.1 was associated with lower general cognitive function at genome-wide significance. Additional studies are required to confirm these findings and explore the role of *TUFM*.

The most significant association with subcortical volumes in young adults was observed for an intergenic variant at chr14q22.3, with *KTN1* as the closest gene, reaching near to genome-wide significance in association with putamen volume despite a limited sample size. Genetic variants in this region had previously been shown to be associated with putamen

shape in healthy adolescents (19), our results thus strengthen the evidence for an important role of this locus in modulating putamen structure across the lifespan.

Noteworthy, genetic correlations between young and older adults were significant for striatal and pallidal volumes only and most significant associations of genetic risk scores and individual variants across age-groups, as well as transcriptome-wide associations were observed for these structures, and to a lesser extent the hippocampus. This could be at least partly explained by the recent observation that striatal and pallidal volumes peak in childhood and decline steadily thereafter, while volumes of the thalamus, amygdala, and hippocampus peak later and start declining from the sixth decade onwards (6). Moreover, interindividual variability of thalamus, amygdala, and hippocampus were found to increase with age, suggesting that these structures may be more susceptible to environmental factors or late-acting genes (6).

Using Mendelian randomization (GSMR), we identified significant associations of genetically determined AD, but not PD, with all subcortical volumes except pallidum in older dementia-free adults, consistent with prior observations from studies using polygenic risk scores of AD on hippocampus and amygdala (50–54). These associations were not observed in young adults, in contrast with other studies, which identified an association between polygenic risk scores of AD and hippocampal volume in adolescent and young adults (22,55). These had used polygenic risk scores composed of SNPs selected at less stringent p-value thresholds (22,55). In young adults we found that genetically determined AD was associated with larger putamen volume and genetically determined PD with larger thalamus volume. If confirmed these results could reflect complex mechanisms whereby biological pathways contributing to larger maximal volumes in certain brain regions early in life could also enhance late-life neurodegenerative processes, akin to the observation that rates of age-related maturation are significantly correlated with rates of decline of white matter tracts (56).

To our knowledge, this is one of the first studies exploring associations of genetic variants with subcortical volumes across the adult lifespan. Our analyses were based on high quality MRI measurements and genome-wide genotype data in several cohorts, including a unique cohort of young students and leverage large scale meta-analyses conducted within the CHARGE consortium. We acknowledge limitations. While we describe trends in heritability estimates, we could not formally compare whether these differed significantly between age groups, therefore decreasing heritability estimates with increasing age need to be interpreted with caution. The sample size of our young adult cohort was limited, particularly compared with the large-scale meta-analysis of GWAS in older adults, and included a majority of women. Our study was restricted to the adult lifespan and should be complemented by cohorts of children and adolescents to capture the full spectrum of genetic determinants across the entire life course. Whereas a longitudinal design would be most appropriate to explore changes in heritability estimates and genetic determinants across the lifespan in the same individuals, repeated MRIs and genetic analyses in large population-based samples are limited and have been available for the past twenty years only. While we show compelling association of genetic risk variants for AD with smaller subcortical volumes in middle and older dementia-free community persons, we did not observe such an association in

young adults. Moreover, while one of the loci associated with lower caudate nucleus volume showed genome-wide significant association with lower general cognitive function, most of the loci associated with subcortical volumes across the adult lifespan were not associated with neurodegenerative diseases after multiple testing correction. This may suggest that these loci are not necessarily reflecting early neurodegenerative processes, but may point to developmental or non-pathological processes related to healthy aging. The fact that genetic loci associated with subcortical volumes in middle-aged to older adults (aggregated in polygenic risk scores) were recently found to be associated with these volumes already during infancy and early childhood could be a potential argument for a stronger role of developmental processes (44). We may have been underpowered to measure the modifying effects (deleterious or protective) of loci modulating subcortical volumes on the occurrence of neurodegenerative diseases. Finally, we cannot exclude selective survival bias for some variants when exploring their relation with late-life neurodegenerative diseases (if variants associated with subcortical volumes also influence survival).

In conclusion, our findings provide novel insight into the genetic determinants of subcortical volumes across the adult lifespan, with some evidence suggesting that specific genes such as *MYLK2* and *TUFM* may have a causal role in determining subcortical volumes already in young adulthood. Further research is warranted to decipher the underlying biological mechanisms and inform prevention strategies for common late-life neurodegenerative diseases, for which pathological processes are known to start long before their clinical diagnosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AD	Alzheimer's disease
eQTL	expression Quantitative Trait Loci
GWAS	Genome-Wide Association Study
LD	Linkage Disequilibrium
LDSR	LD Score Regression
GRS	Genetic Risk Score
MRI	Magnetic Resonance Imaging
PD	Parkinson's disease

SNP	Single Nucleotide Polymorphism
TWAS	Transcriptome-Wide Association Studies

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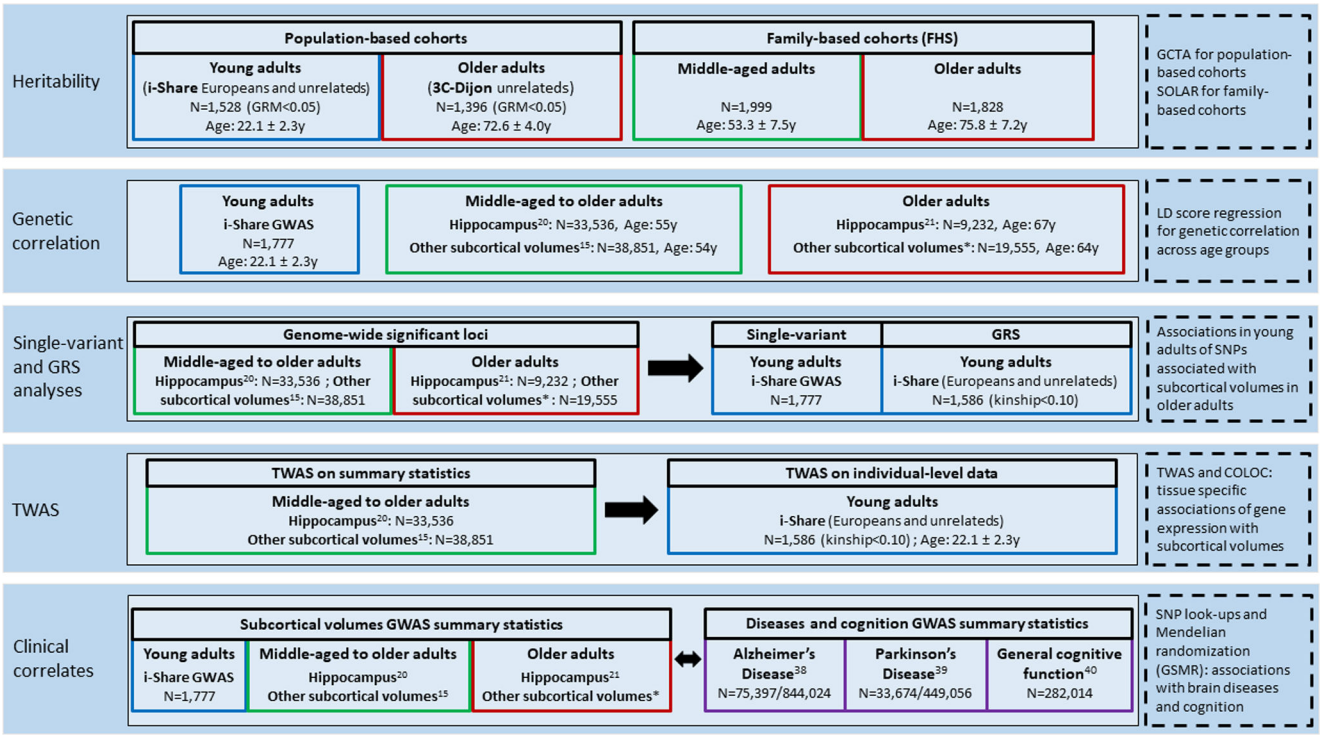

Figure 1: Study workflow and samples summary.

Samples of young adults (18–35) are presented in blue, middle-aged (35–65) to older adults (65+) in green, older adults in red and in purple for disease traits. FHS: Framingham Heart Study. GRM: Genetic relationship matrix. GRS: Genetic risk score. TWAS: Transcriptome-wide association study. [15]: Satizabal et al, Nat Genet 2019. [20]: Hibar et al, Nat Commun 2017. [21]: Bis et al, Nat Genet 2012. [38]: Schwartzentruber et al, Nat Genet 2021. [39]: Nalls et al, Lancet Neurol 2019. [40]: Davies et al, Nat Commun 2018. *: GWAS of subcortical volumes except hippocampal volume after removing ENIGMA and CHARGE cohorts with some young participants (unpublished data).

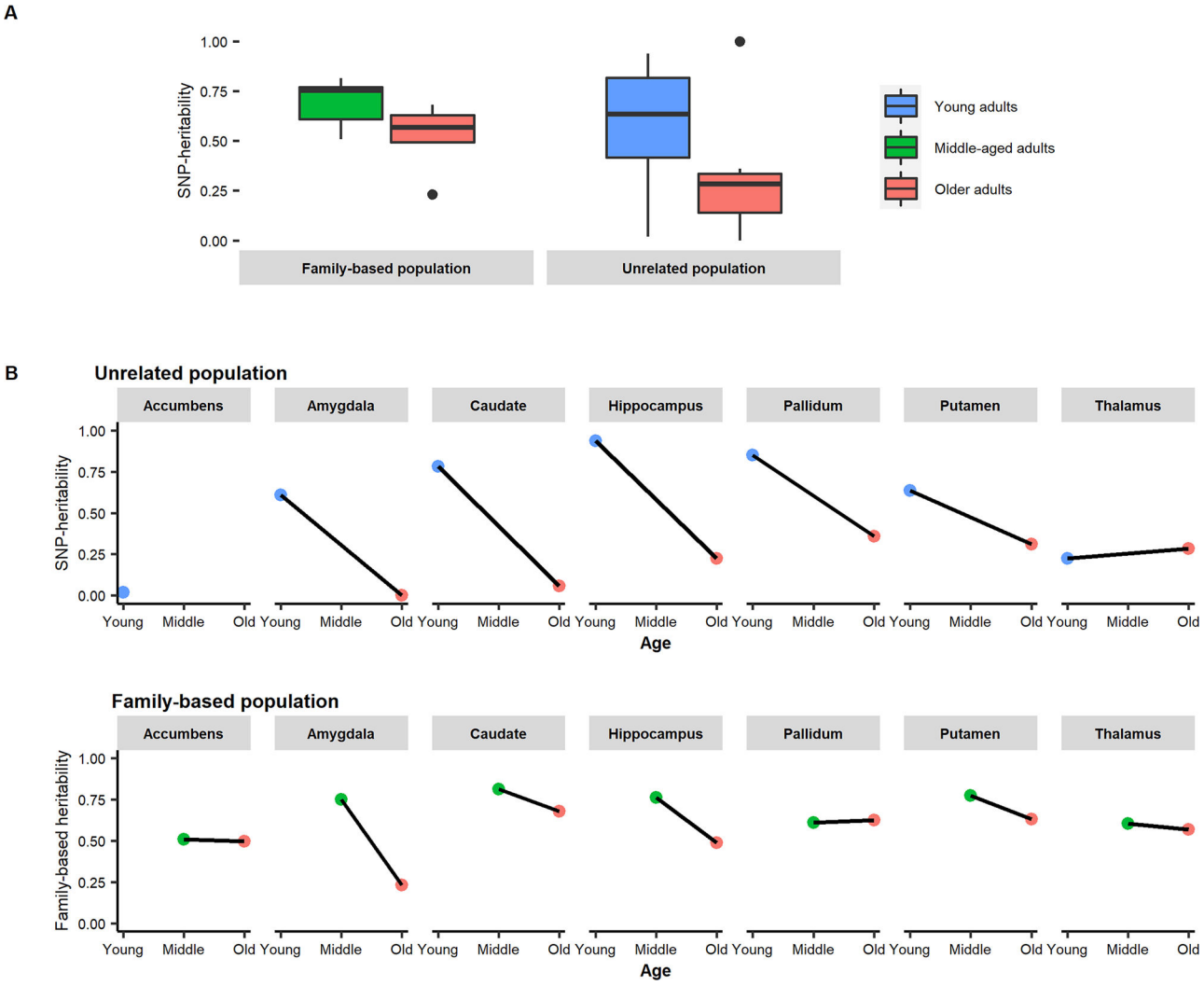

Figure 2: Heritability of subcortical volumes in young adults, middle-aged adults and in older adults.

Panel A: the box plots represent the distribution of the heritability of subcortical volumes. The main rectangle represents the interquartile range and the horizontal line is the median.

Panel B: plot of the estimated SNP heritability for each subcortical volumes, in each age group. For unrelated population, “Young adults” stands for the i-Share cohort (18–35y, N=1,528); “Older adults” stands for the 3C-Dijon cohort (65+, N=1,396). For family-based population, all the groups came from the Framingham Heart Study (three generations). “Middle” or “Middle-aged adults” stands for 36–64y (N=1,999) and “Old” or “Older adults” for 65+ (N=1,828)

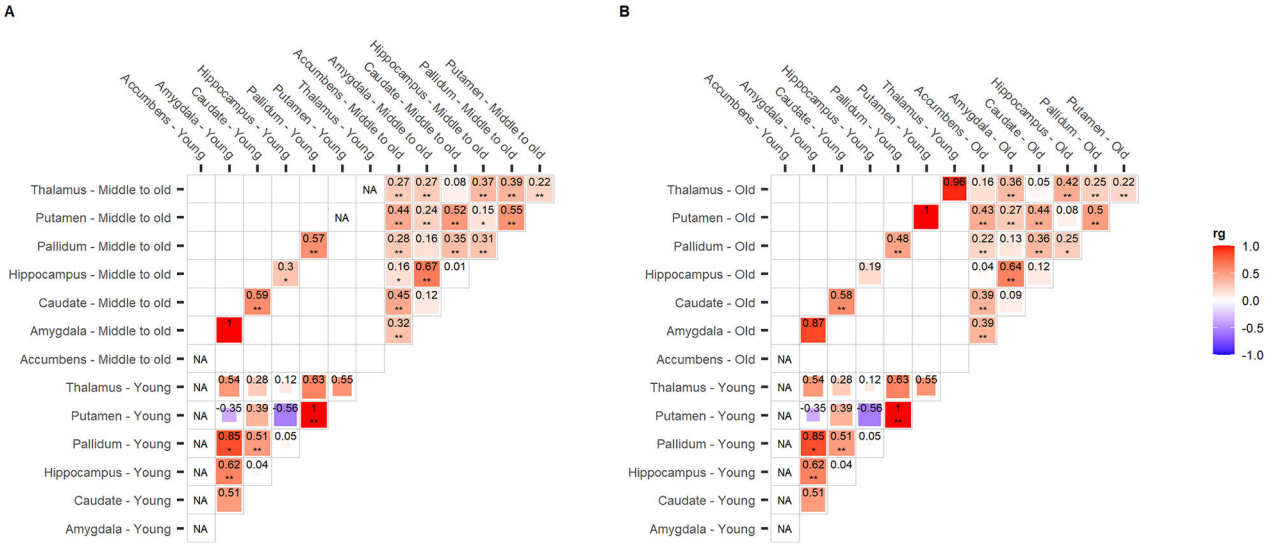

Figure 3: Heatmap of the genetic correlation between subcortical volumes in young adults ("Young"), in older population (Panel A: "Old" and Panel B: "old only") and between the two populations for equivalent structures.

*: nominally significant; **: significant after multiple-testing correction ($p<1.25\times10^{-2}$); Larger colored squares correspond to more significant p-values. In each square, the numbers correspond to the coefficient of the genetic correction (rg). "Young" stands for the i-Share cohort; "Middle to old" for subcortical volumes from the latest largest GWAS (Satizabal et al, Nat Genet 2019 and Hibar et al, Nat Commun 2017); "Old" for the GWAS of subcortical volumes except hippocampal volume after removing ENIGMA and CHARGE cohorts with some young participants and for the CHARGE GWAS of hippocampal volume (Bis et al, Nat Genet 2012)

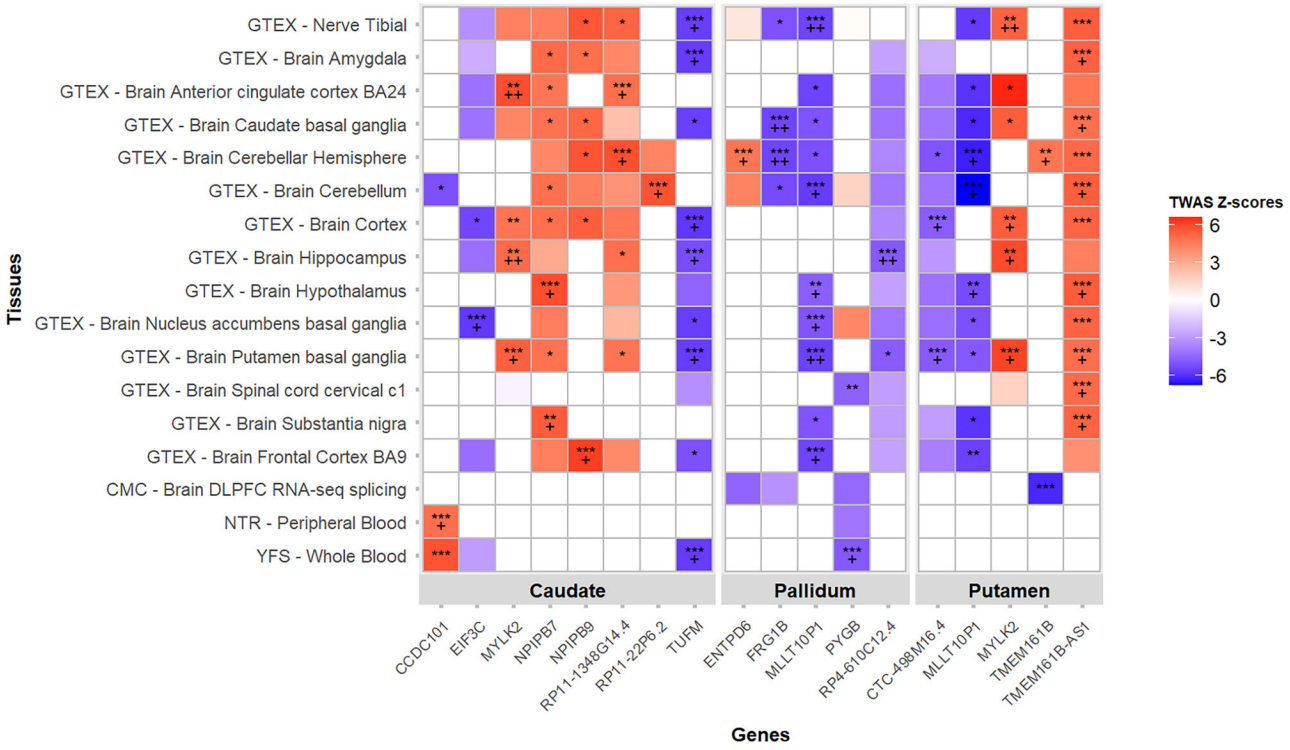

Figure 4: Heatmaps of the transcriptome-wide association studies of the caudate nucleus, putamen and pallidum reaching transcriptome wide significance and colocalized in older persons(15,20) and at least nominal significance in young adults (i-Share cohort).

*: TWAS Significant ($p<3.30\times10^{-6}$); **: Conditionally significant ($p<0.05$); ***: COLOC PP4 > 0.75; +: Nominally significant in i-Share; ++: Significant in i-Share (after multiple-testing correction: accumbens: $p<0.05$; amygdala: $p<0.05$; caudate: $p<2.17\times10^{-3}$; hippocampus: $p<1.67\times10^{-2}$; pallidum: $p<2.94\times10^{-3}$; putamen: $p<3.85\times10^{-3}$; thalamus: $p<0.05$)

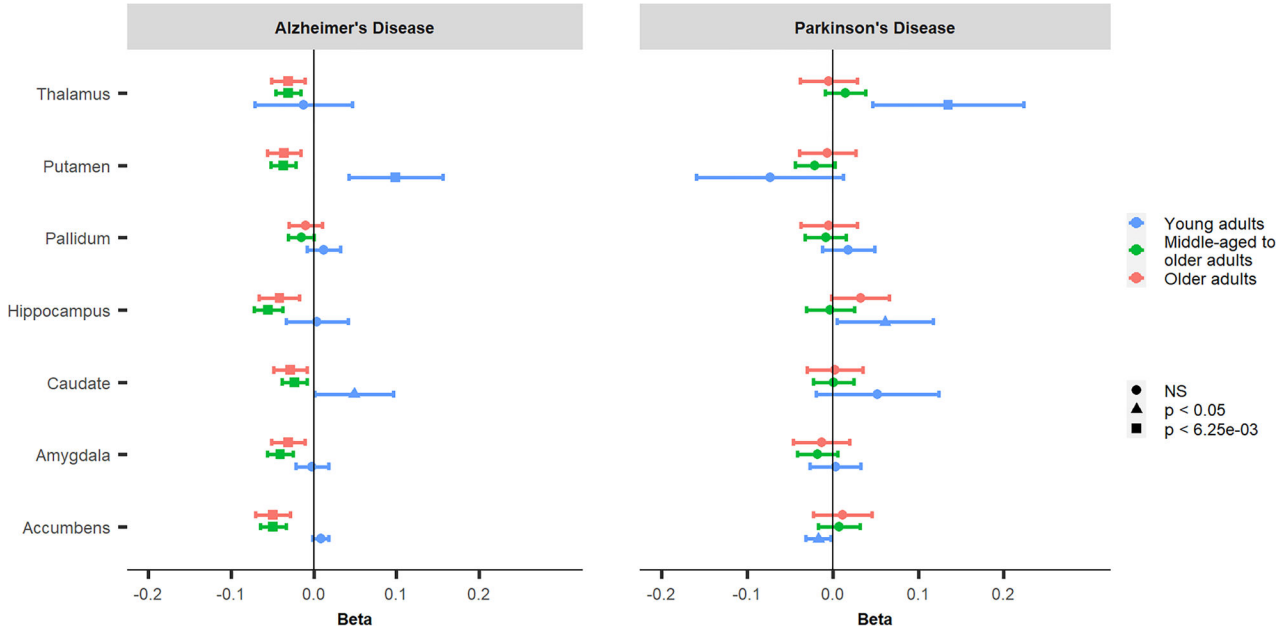

Figure 5: Association between genetically predicted Alzheimer's and Parkinson's diseases and subcortical volumes in young, middle-aged to older and older adults using Mendelian randomization.

"Young adults" stands for the i-Share cohort; "Middle-aged to older adults" for subcortical volumes from the latest largest GWAS (Satizabal et al, Nat Genet 2019 and Hibar et al, Nat Commun 2017); "Older adults" for the GWAS of subcortical volumes except hippocampal volume after removing ENIGMA and CHARGE cohorts with some young participants and for the CHARGE GWAS of hippocampal volume (Bis et al, Nat Genet 2012)

Table 1:

Association of genome-wide significant variants for subcortical volumes in older adults with the same volumes in young adults.

SNP*	Chr	Position	A1	Freq	Nearest genes	Lead SNP from GWAS	Single variant analysis i-Share Cohort (n=1,777)			TWAS analyses† Gene colocalized in the locus‡
							Beta	SE	p	
Amygdala										
rs11111293	12q23.2	102,921,296	C	0.18	IGF1,LINC00485	rs11111293	−0.04	0.01	**4.50E-03**	
Caudate nucleus										
rs10909901	1p36.32	3,131,235	T	0.28	PRDMl6	rs2817145	0.13	0.03	**8.03E-06**	
rsl0830894	11q14.3	92,0l8,778	T	0.41	MIR4490,FAT3	rs3133370	−0.08	0.02	**5.98E-04**	
rs1953353	14q22.3	56,189,751	A	0.32	KTN1,RPL13AP3	rs148470213	−0.10	0.03	**1.92E-04**	
rs4115668	16p11.2	28,607,532	A	0.27	SULT1A2	rs1987471	−0.10	0.03	**1.45E-04**	**CCDC101, NPIPB7, NPIPB9**, SULT1A1, **TUFM, RP11–1348G14.4, RP11–22P6.2**
rs1062794	20q11.21	30,381,758	C	0.34	TPX2	rs6060983	−0.08	0.02	1.59E-03	**MYLK2 (++)**
Hippocampus										
rs17178006	12q14.3	65,718,299	G	0.09	MSRB3	rs61921502	−0.15	0.03	**1.72E-06**	
rs113205216	12q24.22	117,326,943	A	0.09	HRK,FBXW8	rs779563l4	0.12	0.03	**1.41E-04**	
Pallidum										
rs945270	14q22.3	56,200,473	G	0.44	KTN1,RPL13AP3	rsl0l 29414	−0.04	0.01	**2.29E-04**	
rs113818546	20q11.2l	30,369,090	T	0.24	TPX2	rsl0439607	−0.03	0.01	8.46E-03	**ENTPD6, FRG1B (++), MLLT10P1 (++), PYGB**
Putamen										
rs7445l69	5q 14.3	87,703,099	G	0.25	TMEM161B-AS1	rs24l0767	−0.08	0.03	1.25E-02	**CTC-498M 16.4, TMEM161B, TMEM161B-AS1**
rs 12800264	l lq23.3	l 17,396,269	A	0.18	DSCAMLl	rs35200l5	−0.16	0.04	**1.30E-05**	
rs8017172	14q22.3	56,199,048	A	0.44	KTN1,RPL13AP3	rs945270	−0.15	0.03	**1.43E-07**	
rs6060954	20q11.2l	30,383,187	T	0.34	TPX2	rs608777l	−0.08	0.03	5.05E-03	**FRG1B, MLLT10P1, MYLK2 (++)**

Only loci significant in this analysis or in Transcriptome-Wide Association Study in i-Share are presented here.

P-values in **bold** are significant after multiple testing correction (accumbens: $p<3.13\times10^{-3}$; amygdala: $p<1.25\times10^{-2}$; caudate: $p<1.25\times10^{-3}$; hippocampus: $p<2.08\times10^{-3}$; pallidum: $p<2.08\times10^{-3}$; putamen: $p<1.39\times10^{-3}$; thalamus: $p<6.25\times10^{-3}$).

Genes in **bold** are significant in i-Share TWAS and (++) after multiple testing correction (accumbens: $p<0.05$; amygdala: $p<0.05$; caudate: $p<2.17\times10^{-3}$; hippocampus: $p<1.67\times10^{-2}$; pallidum: $p<2.94\times10^{-3}$; putamen: $p<3.85\times10^{-3}$; thalamus: $p<0.05$).

[*] For each locus associated at genome-wide significant level with at least one subcortical structure in Satizabal et al and Hibar et al, associations of the lead SNP and nearby variants (±250 kb) in moderate to high LD (LD-r^2>0.5) with the corresponding phenotype were tested in young adults. Only the top SNP of each locus is presented in this table.

[†] TWAS analyses based on the summary statistics from Satizabal et al, Nat Genet 2019 for subcortical volumes (except hippocampal volume) and from Hibar et al, Nat Commun 2017 for hippocampal volume and results from the i-Share TWAS (n=1,586).

[≠] A gene was considered as in the same locus than the top SNP from the GWAS if at least one of its eQTLs was in LD (r^2> 0.01) with the top SNP

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Table 2:

Association of genetic risk score (from genome-wide significant variants) of subcortical volumes in older adults with the same volumes in young adults.

Genetic Risk Scores (GRS)	i-Share Cohort (n=1,586)		
	Beta	SE	p
Accumbens			
GRS from full GWAS *	−0.04	0.04	3.56E-01
GRS from GWAS old only †	−0.05	0.08	4.69E-01
Amygdala			
GRS from full GWAS *	−0.61	0.14	**9.47E-06**
GRS from GWAS old only †	−0.23	0.15	1.29E-01
Caudate nucleus			
GRS from full GWAS *	−0.73	0.14	**9.76E-08**
GRS from GWAS old only †	−0.99	0.21	**2.31E-06**
Hippocampus			
GRS from full GWAS *	−0.46	0.09	**2.08E-07**
GRS from GWAS old only †	−1.12	0.21	**7.74E-08**
Pallidum			
GRS from full GWAS *	−0.28	0.07	**6.15E-05**
GRS from GWAS old only †	−0.16	0.10	1.20E-01
Putamen			
GRS from full GWAS *	−0.67	0.10	**5.04E-11**
GRS from GWAS old only †	−1.05	0.21	**5.92E-07**
Thalamus			
GRS from full GWAS *	−0.21	0.31	5.01E-01
GRS from GWAS old only †	0.07	0.54	8.98E-01

P-values in **bold** significant results after multiple testing correction ($p < 1.25\times10^{-2}$).

* GRS generated using the SNPs with p<5E-08 from the summary statistics of the GWAS of subcortical volumes from Satizabal et al. Nat Genet 2019 and from Hibar et al, Nat Commun 2017 for hippocampal volume

† GRS generated using the SNPs with p<5E-08 from the summary statistics of the GWAS of subcortical volumes from Satizabal et al. Nat Genet 2019 after excluding cohorts containing young participants and from Bis et al, Nat Genet 2012 for hippocampal volume

Table 3:

Association of genetic variants associated with subcortical volumes in older and young adults with Alzheimer's and Parkinson's diseases and general cognitive function

			Subcortical volumes Young adults *(n=1,777)*		Alzheimer Disease *(n=75,397 / 844,024)*		Parkinson Disease *(n=33,674 / 449,056)*		General cognitive function *(n=282,0l4)*	
SNP	**Locus**	**AI**	**Z**	**p**	**Z**	**p**	**Z**	**p**	**Z**	**p**
Amygdala										
rs11111293	12q23.2	C	−2.84	**4.50E-03**	−0.79	4.28E-01	0.22	8.22E-01	−2.67	7.63E-03
Caudate nucleus										
rs10909901	1p36.32	C	−4.46	**8.03E-06**	−0.07	9.43E-01	−0.64	5.20E-01	−1.49	1.38E-01
rs10830894	11q14.3	T	−3.43	**5.98E-04**	0.20	8.43E-01	−2.l2	3.40E-02	−0.37	7. i 0E-01
rs1953353	14q22.3	A	−3.73	**1.92E-04**	1.46	1.44E-01	−2.60	9.23E-03	−1.60	1.10E-01
rs4115668	16p11.2	A	−3.80	**1.45E-04**	−1.84	6.64E-02	−2.01	4.52E-02	−7.30	**2.88E-13**
rs1062794	20q11.21	C	−3.16	1.59E-03	−1.55	1.22E-01	−1.86	6.19E-02	−0.07	9.48E-01
Hippocampus										
rs17178006	12q14.3	G	−4.78	**1.72E-06**	−2.92	3.49E-03	−1.84	6.53E-02	−0.72	4.75E-01
rs113205216	12q24.22	C	−3.81	**1.41E-04**	−2.10	3.59E-02	−0.31	7.60E-01	0.73	4.68E-01
Pallidum										
rs945270	14q22.3	G	−3.68	**2.29E-04**	1.57	1.17E-01	−2.45	1.47E-02	−2.04	4.16E-02
rs113818546	20q11.21	T	−2.63	8.46E-03	−1.02	3.09E-01	−1.60	1.09E-01	0.10	9.18E-01
Putamen										
rs7445169	5q14.3	G	−2.50	1.25E-02	0.81	4.19E-01	−0.12	9.08E-01	3.63	**2.88E-04**
rs12800264	11q23.3	A	−4.36	**1.30E-05**	−0.75	4.54E-01	−0.20	8.39E-01	0.95	3.44E-01
rs8017172	14q22.3	A	−5.26	**1.43E-07**	1.44	1.49E-01	−2.54	1.10E-02	−1.98	4.77E-02
rs6060954	20q11.21	T	−2.80	5.05E-03	−1.53	1.26E-01	−1.84	6.53E-02	0.00	9.98E-01

Only loci significant in single-variant analysis or in Transcriptome-Wide Association Study in i-Share are presented here.

For subcortical volumes, P-values in **bold** are significant after multiple testing correction (accumbens: $p<3.13\times10^{-3}$; amygdala: $p<1.25\times10^{-2}$; caudate: $p<1.25\times10^{-3}$; hippocampus: $p<2.08\times10^{-3}$; pallidum: $p<2.08\times10^{-3}$; putamen: $p<1.39\times10^{-3}$; thalamus: $p<6.25\times10^{-3}$).

For Alzheimer's and Parkinson's diseases and general cognitive function, p-values in **bold** are significant after correction for multiple-testing ($p< 1.67\times10^{3}$).