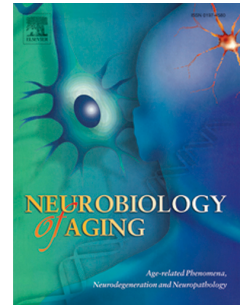


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Polygenic risk for Alzheimer's disease influences precuneal volume in two independent general populations

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Abstract

Alzheimer's disease (AD) is heritable with complex genetic underpinnings. Based on previous results from large-scale genome-wide association studies (GWAS), recent studies found an association between the polygenic risk score (PGRS) of AD and the structure of some preselected brain regions, but the effects of AD PGRS on all voxels of the brain have not been fully investigated. In the current study, we examined the voxel-wise effect of AD PGRS on the entire brain and the influence of AD PGRS on cognitive function in two independent healthy young cohorts. In both cohorts, an elevated AD PGRS was associated with a smaller precuneal volume, and the effect remained after excluding the APOE genotype. No correlation was found between AD PGRS and any cognitive measure in either sample. Finding a negative correlation between the AD PGRS and the precuneal volume could help to elucidate the mechanism of the genetic risk for AD and could provide a potential biomarker for early detection and possible interventions in AD.

Key words: Alzheimer's disease; neuroimaging; polygenic risk score; precuneus

1. Introduction

As many as 60-70% of dementia patients have Alzheimer's disease (AD), making it the most common type of dementia (Duthey, 2013). Treatments to stop or reverse the progression of this disease are not yet available. With the proportion of people aged

60 and over increasing rapidly, the impact of AD on society and public health has caused extensive concern.

The individual risk for AD has complex genetic underpinnings with a heritability estimate of 50-70% (Gatz et al., 1997; Pedersen et al., 2004). Genome-wide association studies (GWAS) identified several common risk variants for AD, but most of these risk alleles only showed a modest effect size (odds ratio [OR] ~ 0.86-1.22) (Lambert et al., 2013; Naj et al., 2011; Seshadri et al., 2010). Therefore, many studies used the polygenetic risk score (PGRS), which combines loci with low effects to identify phenotypic associations. The PGRS enables the identification of phenotypic associations which would not be detectable using single loci with low effect sizes and has been proposed to improve predictive ability and statistical power (Dima and Breen, 2015; Dudbridge, 2013).

The AD PGRS has been found to be associated with the risk of familial late-onset AD (Tosto et al., 2017), accelerated progression from mild cognitive impairment (MCI) to AD (Rodriguez-Rodriguez et al., 2013), cognitive scores (Verhaaren et al., 2013), and neuroimaging measures, including total brain volume (Chauhan et al., 2015), hippocampal volume (Chauhan et al., 2015; Foley et al., 2017; Lupton et al., 2016; Mormino et al., 2016), the cortical thickness in AD-vulnerable regions (Sabuncu et al., 2012), and the fractional anisotropy of the right cingulum (Foley et al., 2017). These studies, especially the neuroimaging studies, help to elucidate the mechanisms of the

genetic contribution to AD risk. However, only a few brain regions have been selected and studied based on a priori hypotheses, and the effects of the PGRS on all voxels of the brain remain unclear. In addition, any early voxel-wise effects of AD risk factors on the brains of healthy young adults before substantial age-related atrophy occurs needs to be clear, since AD pathology begins decades before clinical symptoms (Frisoni et al., 2010; Weiner et al., 2015) and because single genetic variants for AD risk have individually been shown to affect brain structure in young people (O'Dwyer et al., 2012) and infants (Dean et al., 2014).

In the current study, we tested the joint effects of the cumulative AD risk variants on brain structure using a hypothesis-free voxel-wise approach in two independent young healthy samples. The PGRS was computed from the currently largest AD GWAS dataset, comprising 17,008 cases and 37,154 controls, obtained by the International Genomics of Alzheimer's Project (IGAP) (Lambert et al., 2013). We hypothesized that the AD PGRS would be linked to decreased brain volume in AD-vulnerable regions.

2. Methods

2.1. Participants

The discovery dataset recruited a total of 360 healthy young Chinese subjects (174 females, mean age = 19.4 ± 1.1 years) (Li et al., 2015) who, together with their first-, second-, and third-degree relatives, had no history of psychiatric disorder. None of the

subjects had neurological disorders or were taking any medications that could interfere with their ability to complete the MRI scanning. They all gave informed written consent. This study was approved by the Ethics Committee of the School of Life Science and Technology at the University of Electronic Science and Technology of China.

To validate the reliability of the polygenic effect on brain structure, we also recruited an independent dataset. The replication dataset was obtained from a different cohort of subjects and included a total of 323 healthy young Chinese participants (166 females, mean age = 22.7 ± 2.5 years) (Li et al., 2013). None of the subjects had any history of psychiatric diagnoses or of neurological illnesses. This study was approved by the Ethics Committee of Tianjin Medical University. All the subjects gave full written informed consent.

2.2. Genotype Processing

After a blood sample was collected, genomic DNA was extracted by using the E.Z.N.A.TM Blood DNA Kit (Omega Bio-Tek, Georgia, US). Next, Whole-genome genotyping was performed on Illumina Human OmniZhongHua-8 BeadChips (including 900,015 SNP markers and CNV probes) using the standard Illumina genotyping protocol (Illumina). Then the following genotype QCs were performed using PLINK 1.07 (Purcell et al., 2007): First, four individuals with missing genotype rates greater than 0.05 were removed (one from the discovery dataset and three from

the replication dataset). Subsequently, pairwise identity-by-descent (IBD) was estimated to find pairs of individuals who had more similar genotypes than expected by chance in a random sample, and seven subjects (two from the discovery and five from the replication datasets) were additionally removed as they were identified as having possible relative relationships with another person in the dataset and, of the pair, had the higher missing genotype rate. Then, SNP-level filtering was applied; SNPs that met one of the following criteria were removed: a minor allele frequency less than 0.01, missing genotype rates greater than 0.05, or significant departure from Hardy-Weinberg equilibrium ($p < 0.001$). To control for population stratification, a principal component analysis (PCA) was then conducted using EIGENSTRAT 5.0.2 (Patterson et al., 2006; Price et al., 2006) on a linkage disequilibrium (LD) pruned set of autosomal SNPs with the HapMap phase 3 reference data set (Thorisson et al., 2005); and five long-range LD regions were removed. Next, the outliers of the subjects in ten principal components (more than six standard deviations from the mean) were excluded. Ungenotyped SNPs were imputed using SHAPEIT v2 (r790) (Delaneau et al., 2011) and IMPUTE2 (Howie et al., 2009) with the 1000 Genomes Phase 1 reference dataset. Only imputed autosomal SNPs that had imputation quality scores greater than 0.8 were retained. After these QC procedures, a further analysis focused on a total of 357 (discovery dataset) and 315 (replication dataset) subjects with more than 7 million SNPs (see Table 1 for demographic details). We also defined the *APOE* score as ϵ_4/ϵ_2 status ($\epsilon_2/\epsilon_3 = 1$, $\epsilon_3/\epsilon_3 = 2$, $\epsilon_3/\epsilon_4 = 3$) for the subsequent analyses.

2.3. Computation of the PGRS

To compute the polygenic AD-risk score, we used the “score” utility in PLINK (Purcell et al., 2007) and the large meta-GWAS results (Lambert et al., 2013) reported by the International Genomics of Alzheimer’s project (IGAP). First, SNPs that showed a nominal association with AD ($p < 0.05$) from the GWAS results were selected. To account for only independent association signals, LD pruning was then conducted using the clumping utility in PLINK with an LD $r^2 < 0.25$ within a 500 bp window, and the index SNPs were extracted using the most significant association p -value within each clumped region. The index SNP list was acquired and SNPs with a minor allele frequency < 0.01 in the target sample were further removed; the remained SNPs were used to calculate the PGRS. Finally, the polygenic scores were computed as the summation of an individual’s genotype across the obtained SNP list, which consisted of 60,263 independent SNPs weighted by the effect size estimated based on the IGAP GWAS (see Supplementary Table S1 for SNP information). An unweighted score was constructed by summing the number of AD-associated alleles across selected markers without considering their effect sizes.

2.4. MRI Data Acquisition and Processing

MRI scans for the two independent datasets were performed using the following parameters: in the discovery dataset, TR = 8.16 ms, TE = 3.18 ms, flip angle = 7° , FOV = $256 \text{ mm} \times 256 \text{ mm}^2$, voxel size = $1 \times 1 \times 1 \text{ mm}^3$, and 188 slices in an MR750

3.0 Tesla magnetic resonance scanner (GE Healthcare); in the replication dataset, TR = 8.1 ms, TE = 3.1 ms, flip angle = 13° , FOV = $256 \times 256 \text{ mm}^2$, voxel size = $1 \times 1 \times 1 \text{ mm}^3$, and 176 slices in a 3.0 T Signa HDx GE scanner. All the raw MRI data were then inspected by two experienced radiologists who were blind to the PGRS information.

The structural MRI scans were processed using the Diffeomorphic Anatomical Registration Through the Exponentiated Lie Algebra (DARTEL) -based VBM (Ashburner, 2007) toolbox (<http://dbm.neuro.uni-hen.de/vbm>) in SPM8 (Wellcome Department of Imaging Neuroscience, London, UK, <http://www.fil.ion.ucl.ac.uk/spm>) executed in MATLAB 2013a (The MathWorks, Natick, MA). Following segmentation, gray matter (GM) templates were generated using the entire image dataset. The GM template was initially affine registered to the tissue probability map in Montreal Neurological Institute (MNI) space, and the GM images were non-linearly warped to the GM template in MNI space. The GM segments were modulated by using the affine and non-linear components, and the actual gray-matter values (modulated GM volumes) were generated locally. The modulated GM segments were then smoothed using a Gaussian kernel of 8 mm full width at half maximum. After these steps, we obtained the normalized, modulated, and smoothed gray-matter maps. The value of each voxel reflected the volume information with spatial deformation and was used for later statistical analyses. In addition, the gray matter, white matter, and CSF volumes in the native MRI brain scan for each subject

were standard outputs; so an estimate of the total intracranial volume (eTIV) was calculated as the sum of the three volumes. Two of 315 subjects in the replication sample were excluded because of excessive head motion during the T1 scans. The final sample for the gene-brain analyses included 357 subjects in the discovery dataset and 313 individuals in the replication dataset.

2.5. Cognitive Tests

All subjects took the Chinese Revised Wechsler Adult Intelligence Scale (WAIS-RC) (Gong, 1982) and performed the working memory (WM) tasks with an N-back paradigm (2- and 3-back), as described in our previous study (Li et al., 2015). In brief, the participants were continuously presented with a series of letters and were asked to decide whether the letter presented on the screen was the same as the one presented two letters earlier (for the 2-back task) or the one presented three letters earlier (for the 3-back task). Both the 2-back and 3-back tasks consisted of 3 blocks of 30 trials each, and all six blocks were presented randomly to each subject. Before the experiment, the participants were given verbal instructions followed by one practice block for each task. They had to pass 70% of the trials before they could take the real tests. Both the IQ test and the WM tasks were performed on a computer in a quiet room outside the MRI scanner.

2.6. Statistical Analysis

The association between the PGRS and the gray matter volume was analyzed separately in 2 datasets using SPM8. In both samples, the correlation was tested using

voxel-wise multiple regression models with age, gender, and the eTIV as covariates. The statistical result of was corrected for multiple comparisons using the “AlphaSim” implementation in REST Toolkit (Song et al., 2011), which is based on the Monte Carlo simulation in AFNI (see the AlphaSim command description at <http://afni.nimh.nih.gov/afni/doc/manual/AlphaSim>) in the discovery dataset. Correlation was reported at $p < 0.001$ (uncorrected), cluster size > 50 for the replication dataset. Then the correlation between the PGRS and the three cognitive measures (IQ, WM 2-, and 3-back performance) was calculated using a regression analysis with gender and age as covariates for the 2 datasets separately. The regression analyses with cognitive performance were carried out in IBM SPSS statistics 22 (IBM Corp., Armonk, NY) for Windows.

3. Results

3.1. Association between the PGRS and Brain Volume in the Discovery Dataset

The whole-brain VBM analyses showed a significant negative correlation (corrected $p < 0.05$) between the PGRS and gray matter volume (GMV) in the left precuneus (peak MNI coordinates $x = -12$, $y = -51$, $z = 58.5$, 166 voxels, peak $T = -4.01$) and the right cingulate gyrus (peak MNI coordinates $x = 6$, $y = 3$, $z = 33$, 188 voxels, peak $T = -3.81$) and a significant positive correlation between the AD PGRS and the GMV in the right superior frontal gyrus (peak MNI coordinates $x = 6$, $y = 66$, $z = 1.5$, 472 voxels, peak $T = 4.48$) and the right caudate (peak MNI coordinates $x = -1.5$, $y = 4.5$, $z = 1.5$, 418 voxels, peak $T = 4.10$) (Figure 1). This suggested that subjects in the

discovery set with a higher AD PGRS had a smaller GMV in the left precuneus and right cingulate gyrus and a larger GMV in the right superior frontal gyrus and right caudate.

3.2. Association between the PGRS and the Brain Volume in the Replication Dataset

Regression analysis between the PGRS and brain volume was carried out using a voxel-wise multiple regression model in the replication sample. Only the left precuneus (peak MNI coordinates $x = -4.5$, $y = -72$, $z = 46.5$, 90 voxels, peak $T = -3.61$) reached significance (uncorrected $p < 0.001$, $k > 50$) and showed a negative correlation with the PGRS (Figure 2). This supported the conclusion in the discovery dataset that subjects with a higher genetic risk for AD had a smaller gray matter volume in the precuneus.

3.3. Association between the PGRS and the extracted precuneal volume in both datasets

The left precuneus was found to be associated with the AD PGRS in both cohorts. Next, the average GMVs of the affected precuneus were extracted, and linear regressions with the PGRS as the predictor for the precuneal volume were carried out with age, gender, and eTIV as covariates. We found that the AD PGRS is significantly associated with the GMV of the precuneus (in the discovery dataset, $T = -4.05$, $p = 6.36 \times 10^{-5}$; in the replication dataset, $T = -3.71$, $p = 2.48 \times 10^{-4}$) (Figure 3). To determine whether the effect of the PGRS on the precuneal volume was

independent of the APOE genotype, the APOE genotype was added to the regression model as a covariate. The effect of the PGRS on the GMV of the precuneus remained significant (in the discovery dataset, $T = -3.89$, $p = 1.22 \times 10^{-4}$; in the replication dataset, $T = -3.57$, $p = 4.16 \times 10^{-4}$). These results suggested that the relationship between the AD PGRS and the precuneal volume is not exclusively affected by the APOE gene but by multiple genetic factors.

To ensure that the association was not affected by education or population stratification, we also included years of education and the first ten principal components estimated from our GWAS data as covariates with age, gender, and eTIV in the regression model in both datasets. The results showed the association between the PGRS and the GMV of the precuneus remained significant (in the discovery dataset, $T = -4.08$, $p = 5.52 \times 10^{-5}$; in the replication dataset, $T = -3.17$, $p = 1.71 \times 10^{-3}$).

Finally, we conducted analyses with an unweighted PGRS to ascertain whether the associations differed by weighting strategy. Linear regression analyses were conducted for the precuneal volume with the unweighted AD PGRS as predictors, with age, gender, years of education, eTIV and the first ten principal components estimated from our GWAS data as covariates in both datasets, separately. These results showed that the association between the unweighted AD PGRS and the precuneal volume was significant only in the discovery dataset (in the discovery dataset, $T = -2.16$, $p = 0.031$; in the replication dataset, $T = -1.21$, $p = 0.23$). Then a

fixed-effect meta-analysis based on these results was performed. We found a significant negative association between the unweighted AD PGRS and the precuneal volume (pooled beta = -0.083, 95% CI: -0.15 to -0.015, $p = 0.016$; Figure S1).

3.4. Association between the PGRS and Cognitive Measures in Both Datasets

To test the effect of polygenic risk for AD on cognitive function, regression analyses were carried out for both cohorts. No associations were found between the AD PGRS and cognitive variables (IQ or working memory 2- and 3-back) (all $ps > 0.05$; Table 2) in either the discovery or the replication dataset. Then years of education and the first ten principal components estimated from our GWAS data were added as covariates in the regression model in both datasets, no associations were found between the AD PGRS and cognitive variables (IQ or working memory 2- and 3-back) (all $ps > 0.05$; Supplementary Table S2) in either dataset.

4. Discussion

By combining structural MRI and genome-wide genetic data from two independent young cohorts, we found a consistent negative correlation between the AD PGRS and the left precuneal volume, a brain region which is preferentially vulnerable to AD (Ryu et al., 2010; Sperling et al., 2009). This suggested an effect of AD PGRS on brain structure several decades before any possible clinical symptoms of AD could develop and may provide implications for the genetic mechanisms underlying AD pathology.

Several studies have examined the influence of the AD PGRS on brain structure. These studies tested the association between the polygenic risk for AD and hippocampal volume and found this association in a large population-based meta-analysis in healthy older adults and MCI subjects (Lupton et al., 2016; Mormino et al., 2016). This association was validated in one young cohort (Foley et al., 2017) but not in another young sample (Lupton et al., 2016). The effect of the AD PGRS on the cortical thickness of some AD-vulnerable regions in healthy older (Sabuncu et al., 2012) and young individuals (Foley et al., 2017), on the fractional anisotropy of the right cingulum in healthy young adults (Foley et al., 2017), and on total brain volume in dementia-free participants (Chauhan et al., 2015) were also reported. These studies confirmed the influence of the polygenic risk for AD on some MRI-based intermediate phenotypes of AD in the general population. However, these studies all focused only on preselected regions, while possible structural changes in other areas remained unknown. In addition, they could not tell us at what age the influences of the AD PGRS on the entire brain structure initially manifest. The current study used a hypothesis-free VBM analysis, which has been widely used to detect structural atrophy in individuals with AD (Shimoda et al., 2015; Whitwell et al., 2008), to estimate the effect of the AD PGRS on voxel-wise anatomical differences by exploring the whole brain. Using this data-driven approach, we showed that the AD PGRS seems to have influenced the volume of several cortical structures that had not been reported in previous ROI studies. Additionally, by recruiting young samples, we

also found that these AD-related brain structures were modulated by the polygenic risk for AD even in young adults.

One especially interesting finding of our study was the negative association between the AD PGRS and the left precuneal volume in both datasets. This was expected because the precuneus is a pivotal region for the disease process of AD. The precuneus is preferentially affected pathologically (Sperling et al., 2009), structurally (Ryu et al., 2010), and functionally (Sadigh-Eteghad et al., 2014) in AD. Compared with controls, AD patients exhibit significant atrophy (Migliaccio et al., 2009; Ryu et al., 2010) and a greater progressive volume change (Scheinin et al., 2009) in the precuneus. Other studies also observed decreased glucose metabolism (Pascual et al., 2010) and hypoperfusion (Hu et al., 2010) in the precuneus and reduced functional connectivity between the precuneus and other AD vulnerable regions (Kim et al., 2013) in AD patients compared to controls. In addition, structural features of the precuneus are one of the key biomarkers for optimizing the classification of MCI subjects into those who will convert to AD and those who will remain stable (Whitwell et al., 2008; Zhuang et al., 2012) and for discriminating between AD and frontotemporal lobar degeneration (McMillan et al., 2012). Moreover, studies have consistently found a significantly lower gray matter volume of the precuneus in subjects who were symptomatic familial Alzheimer disease mutation carriers (Cash et al., 2013), in cognitively healthy individuals with a family history of AD (Honea et al., 2010), and even in infant carriers of AD genetic risk (APOE e4) (Dean et al., 2014).

Our results are in line with those from these studies, and together they suggest that the structure of the precuneus can be used as a preferred endophenotype for imaging genetics studies of the polygenic risk for AD.

Many brain regions that have previously been reported to be affected in AD were not associated with the AD PGRS in the current study. One possible explanation is that the genetic risk of AD may impact those brain regions in older subjects (used in most previous studies) but not in young adults. We were not surprised at this negative result in our sample, as several studies have reported no association between the genetic risk of AD and the structure of brain regions affected in AD in young subjects (Lupton et al., 2016; Richter-Schmidinger et al., 2011). Moreover, smaller precuneal volume was reported in infant *APOE* $\epsilon 4$ carriers (Dean et al., 2014), indicating that the alteration of the precuneal structure is an early effect of the genetic predisposition for AD. Another potential reason is a lack of power in the current study. Using the AVENGEME package (Palla and Dudbridge, 2015), we calculated the power and found that we had 80% power to detect an effect ranging from 0.0215 to 0.0245 of the explained variance in our samples ($N = 313-357$). Given the effect sizes/explained variance of the PGRS calculated by previous studies about other AD related brain regions in young adults (Lupton et al., 2016), this study did not have sufficient power to determine small effect sizes of AD PGRS on those brain regions. Therefore, to obtain confirmatory evidence, future studies in samples with different age groups and with larger sample sizes are needed to test this association.

No effect of AD PGRS on cognitive performance was observed in our study. Previous studies of older subjects found that an elevated AD PGRS was associated with worse memory at baseline (Mormino et al., 2016) and with greater longitudinal cognitive decline over time (Louwersheimer et al., 2016). Age differences may explain the lack of a significant association between AD genetic risk and the cognitive measures in the current study. These results together suggested that the polygenic risk of AD influence AD-vulnerable brain regions decades before cognitive impairments can be detected. This may further indicate that brain volume is a more sensitive imaging marker for AD genetic risk than the cognitive measures tested here.

There are several limitations: First of all, we calculated the AD PGRS for two Han Chinese samples using the GWAS result from Caucasian samples due to the lack of GWA study on Han Chinese samples, and to our knowledge, this is currently the largest AD GWAS dataset. In our analysis, we considered both weighted and unweighted risk scores to ensure that the use of Caucasian-derived SNPs weights did not affect the results. We found a consistent negative association between the AD PGRS and the precuneal volume using either a weighting or an unweighting strategy. Several studies have reported that the genetic risk score based on one ethnic population can translate to other ethnic groups (Domingue et al., 2014; Ikeda et al., 2011; Marden et al., 2014). These studies expanded the scope of the research to other populations and indicated that the PGRS is a useful approach for trans-ethnic

replication of genetic associations. Overall, our study generalized observations of a genetic basis for AD to populations with a different ethnicity. Further studies are needed to recalculate the AD PGRS once GWAS studies on Han Chinese samples are available. Besides, studies with larger populations to increase the statistical power and new approaches to increase the accuracy of the PGRS analysis in diverse populations are required (Marquez-Luna et al., 2017).

Second, the current study used a conservative significance threshold (AlphaSim $p < 0.05$ in the discovery sample and uncorrected $p < 0.001$ in the replicate sample), but this may not be sufficient. Regardless, given the exploratory nature of the study, it is plausible to use a permissive approach to avoid rejecting possibly interesting results. Further studies are needed to confirm these results. Third, although the precuneal regions extracted from the discovery sample and from the replication sample did not completely overlap, they consistently demonstrated a negative association between the polygenic risk for AD and the volume in the precuneal region and could help us understand the neurodegenerative process decades before the onset of clinical symptoms of AD. More evidence and replication studies are therefore needed. Fourth, how these brain measures change with age is unknown. Therefore, longitudinal studies are needed to follow healthy young adults over ten or more years to determine whether the decreased precuneal volume is followed by a higher risk of developing later pathological changes.

In summary, we showed that the AD polygenic score was associated with reduced volume in the left precuneus in two young, healthy groups. This association provides a mechanism for vulnerability to AD progression in people with a higher genetic risk for AD. These results also suggest that precuneal morphology might be an early biomarker for the prediction and possible prevention and treatment of AD.

Disclosure statement

The authors have no conflicts of interest to disclose.

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Tables

Table 1. Demographic characteristics of the participants

	Discovery dataset	Replication dataset
Subjects	357	315
Sex (male/female)	183:174	154:161
Age (y)	19.41 ± 1.17	22.73 ± 2.48
Age range (y)	18-24	18-31

Values denote mean \pm standard deviation or number of subjects.

Table 2. Regression analyses between the AD PGRS and cognitive characteristics

	Beta	se	T	p
Discovery dataset (n = 357)				
IQ	-0.011	0.049	-0.233	0.816
Working memory 2-back	-0.068	0.053	-1.294	0.196
Working memory 3-back	-0.061	0.053	-1.155	0.249
Replication dataset (n = 315)				
IQ	-0.015	0.056	-0.274	0.784
Working memory 2-back	0.008	0.056	0.149	0.882
Working memory 3-back	0.001	0.057	0.019	0.985

Figures legends

Figure 1

Regions showing a significant association between GMV and AD PGRS in the discovery dataset. Whole-brain voxel-based morphometry showed that the AD PGRS score showed a significantly positive correlation with the right caudate and right superior frontal gyrus and a significantly negative correlation with the right cingulate gyrus and left precuneus (AlphaSim corrected $p < 0.05$, using a voxel-level threshold of uncorrected $p < 0.001$ and a cluster threshold of $k > 143$ voxels).

Figure 2

The left precuneus showed a significant association between GMV and AD PGRS in both datasets. Whole-brain voxel-based morphometry showed that the AD PGRS score was significantly negatively correlated with a region in the left precuneus in (a) the discovery (AlphaSim corrected $p < 0.05$, using a voxel-level threshold of $p < 0.001$ and a cluster threshold of $k > 143$ voxels) and (b) the replication (using a voxel-level threshold of $p < 0.001$ and a cluster threshold of $k > 50$ voxels) datasets.

Figure 3**Individual AD PGRS and GMV in the left affected precuneus in both datasets.**

Extracted individual gray-matter volume in the affected left precuneus was significantly negatively associated with the PGRS for AD in both (a) the discovery dataset and (b) the replication dataset.

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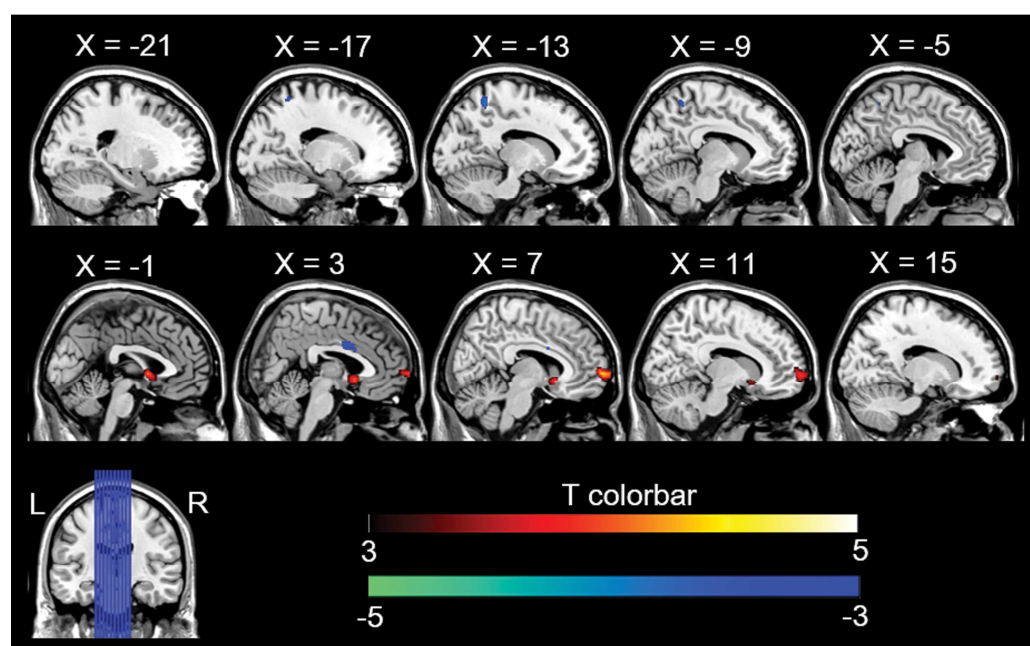
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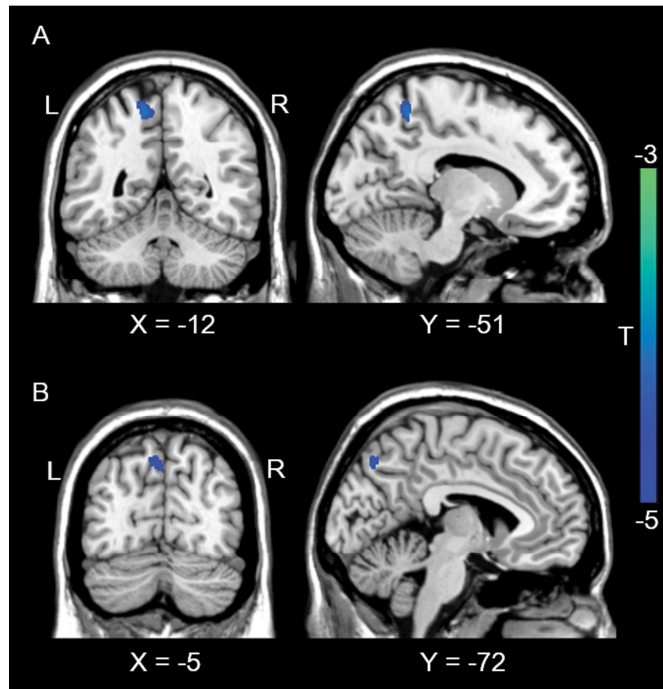
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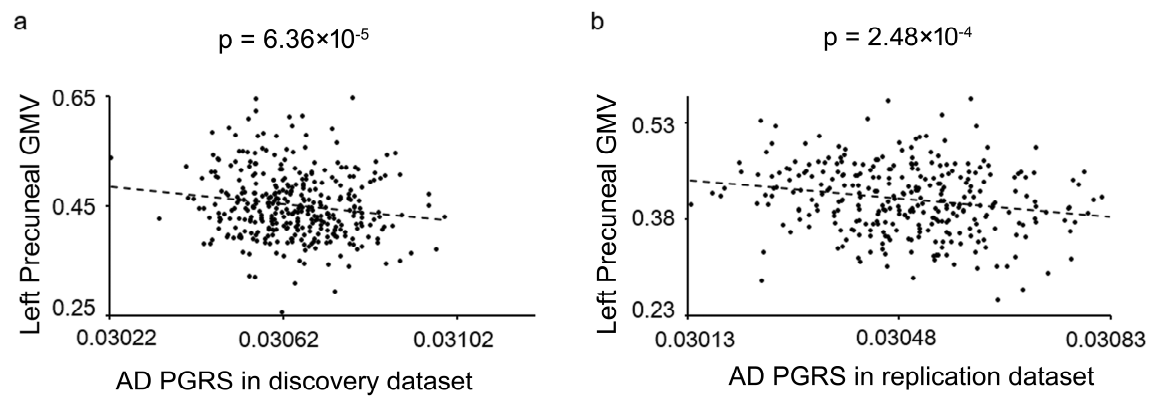
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Highlights

The effect of Alzheimer's disease (AD) polygenic score (PGRS) on brain structure was investigated with a hypotheses-free method.

The precuneal volume is mediated by the genetic risk of AD in two independent cohorts.

AD PGRS modulates the precuneal structure decades before any clinical expression of AD.

Verification

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3. Please verify that the data contained in the manuscript being submitted have not been previously published, have not been submitted elsewhere and will not be submitted elsewhere while under consideration at Neurobiology of Aging.

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4. When applicable, provide statements verifying that appropriate approval and procedures were used concerning human subjects and animals.

The current study recruited two independent datasets, they were approved by the Ethics Committee of the School of Life Science and Technology at the University of Electronic Science and Technology of China, and the Ethics Committee of Tianjin Medical University, respectively.

5. Please verify that all authors have reviewed the contents of the manuscript being submitted, approve of its contents and validate the accuracy of the data.

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