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Introduction

Subcortical brain structures play important roles in neurodegenerative processes, including Alzheimer’s disease (AD), the most common cause of dementia. However, the associations between subcortical brain volumes and AD risk are uncertain and may influenced by age and *APOE* genotype. Polygenic scores (PGSs) for subcortical structures capture the genetic predisposition to structural variation and provide approach to investigate genetic factors related to AD. We aim to investigate the interactions between subcortical structural volume PGSs, age and *APOE* genotype on AD risk.

Methods

Figure 1 Study workflow

Brain Volume Polygenic Scores Generation

Base Data

ENIGMA Subcortical Brain Volumes GWAS Summary Statistics (García-Marín et al. 2024)

Target Cohorts

NIA/LOAD cohort (dbGap accession: phs000168.v2.p2; AD Cases/Controls = 1057/720)
GenADA cohort (dbGap accession: phs000219.v1.p1; AD Cases/Controls = 799/778)

Interaction Models Fit Evaluation

Logistic Regression Models

a. AD Diag ~ PGS + APOE + Sex + 10PCs + Age + Age²
b. AD Diag ~ PGS + APOE + Sex + 10PCs + Age + Age² + PGS × Age + PGS × Age²
c. AD Diag ~ PGS + APOE + Sex + 10PCs + Age + Age² + APOE × Age + APOE × Age²
d. AD Diag ~ PGS + APOE + Sex + 10PCs + Age + Age² + PGS × APOE
e. AD Diag ~ PGS + APOE + Sex + 10PCs + Age + Age² + APOE × Age + APOE × Age² + PGS × Age + PGS × Age²
f. AD Diag ~ PGS + APOE + Sex + 10PCs + Age + Age² + PGS × Age + PGS × Age² + APOE × Age + APOE × Age² + PGS × APOE
g. AD Diag ~ PGS + APOE + Sex + 10PCs + Age + Age² + PGS × Age + PGS × Age² + APOE × Age + APOE × Age² + PGS × APOE + PGS × APOE × Age + PGS × APOE × Age²

Akaike Information Criterion-Corrected Statistic

Lower AICc indicate better fit

Likelihood Ratio Test

P < 0.05 indicate statistically significant

❖ PGSs were constructed using ENIGMA subcortical genome-wide association study (GWAS) summary statistics.

• Discovery cohort: NIA/LOAD (1057 AD cases, 720 controls)

• Replicate cohort: GenADA (799 AD cases, 778 controls)

• PGS threshold: 5e-8 (with *APOE* region SNPs removed)

• Subcortical structures: brainstem, caudate nucleus, putamen, hippocampus, globus pallidus, thalamus, nucleus accumbens, amygdala and ventral diencephalon

❖ Full model (model g) best fit indicating the evidence of PGS × *APOE* ε4 × age interaction.

❖ Sensitivity analyses: alternative PGS thresholds (1e-5, 1e-3, 0.01, 0.1, 1)

Results

- ❖ Discovery NIA/LOAD cohort
 - Among nine subcortical structures, three-way interaction full model was only best fit for nucleus accumbens volume.
 - As shown in Table 1, the AICc for model g was smallest indicating three-way interaction model fits best.
 - Based on LRTs, model g was statistically significant compared with other models showing evidence of three-way interaction.
 - The nucleus accumbens PGS × *APOE* ε4 × age interaction was significantly associated with AD diagnosis (PGS × *APOE* ε4 × age, *P* = 0.009; PGS × *APOE* ε4 × age², *P* = 0.015).
 - Sensitivity analyses using alternative PGS thresholds did not support the nucleus accumbens PGS × *APOE* ε4 × age interaction on AD diagnosis.
- ❖ Replicate GenADA cohort
 - The only significant finding for nucleus accumbens in NIA/LOAD cohort was failed to replicate.
- ❖ Model a which tested the main effect of PGS adding *APOE* ε4, sex, age and first ten principal components of population genetics as covariates did not provide significant association between brain volume PGSs and AD diagnosis.

Table 1 Model fit statistics results for nucleus accumbens volume in NIA/LOAD cohort

Model	K	AICc	ΔAICc	AICcWt	LL	LRT	P
Nucleus accumbens (PRS threshold 5e-8)							
a. Main effect of PGS, APOE, and Age alone	16	2116.04	22.71	0.00	-1041.86	37.03	0.00
b. Main effect of APOE + Age × PGS interaction	18	2118.60	25.27	0.00	-1041.10	35.51	0.00
c. Main effect of PGS + Age × APOE interaction	18	2098.29	4.96	0.06	-1030.95	15.20	0.01
d. Main effect of Age + PGS × APOE interaction	17	2112.69	19.36	0.00	-1039.17	31.64	0.00
e. Age × APOE interaction + Age × APOE interaction	20	2101.02	7.69	0.02	-1030.27	13.84	0.00
f. Age × APOE interaction + Age × APOE interaction + PGS × APOE interaction	21	2096.25	2.93	0.17	-1026.86	7.03	0.03
g. PGS × APOE × Age interaction	23	2093.33	0.00	0.75	-1023.35	-	-

Note: K, number of estimated parameters; AICc, Akaike information criterion-corrected; ΔAICc, difference in AICc between tested model and three-way interaction model (model g); AICcWt, the probability that tested model is best fit; LL, log-likelihood; LRT, likelihood ratio test for comparing tested model and three-way interaction model; P, p value obtained from chi-square.

Conclusions

This study provides limited evidence for *APOE* ε4 modifies the association between subcortical brain volume PGS and age on AD diagnosis. The significant findings in discovery cohort failing replicate in another independent cohort suggest the PGS × *APOE* ε4 × age interaction may be cohort-specific or overestimated. Future study will focus on testing the association between AD polygenic risk scores and subcortical brain volumes.

References

[1] Xu *et al.* Alzheimer’s & Dementia. 2024.
[2] García-Marín *et al.* Nature Genetics. 2024.

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