

Detecting Structural Brain Vulnerabilities in Cognitively Normal APOE4 Carriers Using Interpretable Deep Learning

P4-07

Dan Pan, Rumeng Huang, An Zeng, Jiayu Ye, Baichuan Zhang, Xiaowei Song

We used an interpretable ensemble 3DCNN framework to derive structural MRI-based P-scores for quantifying regional brain structural anomalies in cognitively normal older adults. By comparing cognitively normal APOE4 carriers and non-carriers, this study identifies P-score-defined brain regions showing early structural vulnerability associated with APOE4 genetic risk.



INTRODUCTION

APOE4 is a major genetic risk factor for Alzheimer's disease (AD). Brain structural alterations in cognitively normal older adults carrying the APOE4 allele remain poorly understood.

Objectives:

- ✓ Characterize brain structural alteration patterns.
- ✓ Provide evidence for early AD warning and risk stratification.

METHODS

An interpretable DL technique (Ensemble 3DCNN)

- ✓ **Interpretable Ensemble 3DCNN framework** to generate P-score for quantifying regional structural anomalies.
- ✓ **Compared alteration patterns with P-score thresholds:** 2.0, 1.5, 0.6 times of the standard deviation (SD).

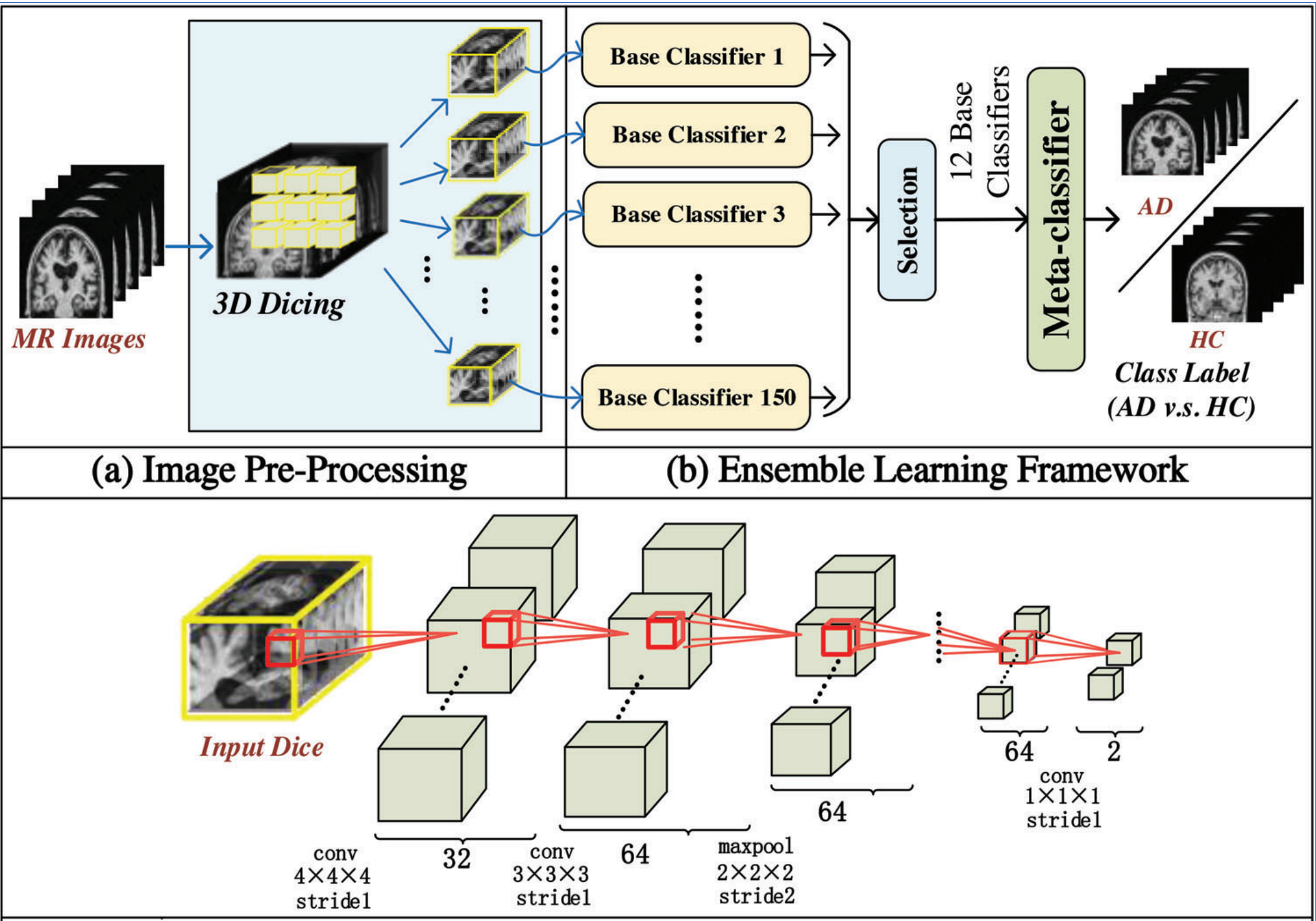


Figure 1. Illustration of the ensemble 3DCNN model.

Table 1. Dataset used in 3DCNN model.

Dataset	Database	Samples (AD : HC)
Training	ADNI	136 : 162
Validation (for analysis)	ADNI	101 : 100
Testing (for analysis)	OASIS	253 : 253

The AD/HC datasets were used to train and validate the P-score model; the APOE4 analysis was then conducted in cognitively normal HC subjects.

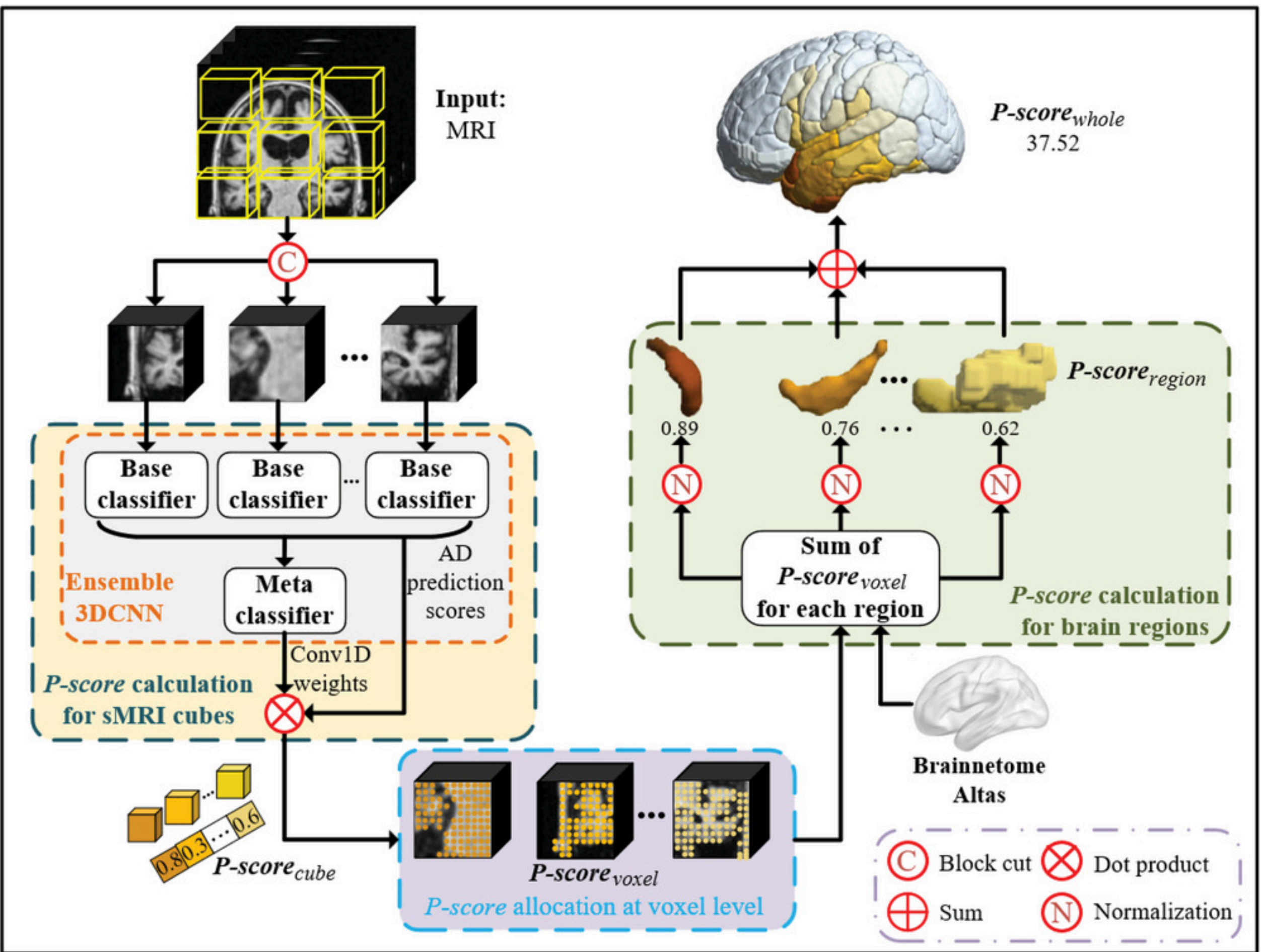


Figure 2. Illustration of P-score calculation at different levels.

Table 2. Dataset used for APOE4 carrier analysis.

Database	Group	(APOE4+ : APOE4-)
ADNI	HC	39 : 52

RESULTS

Table 3. Ranking of brain region differences at P-score threshold 2.0.

Brain Region	APOE4+	APOE4-	Diff (%)
212 {R. mAmyg}	57.8	33.3	24.5
211 {L. mAmyg}	62.5	43.3	19.2
116 {R. A28/34}	39.1	20	19.1
224 {R. NAC}	46.9	28.9	18.0
223 {L. NAC}	54.7	38.9	15.8

Table 4. Ranking of brain region differences at P-score threshold 1.5.

Brain Region	APOE4+	APOE4-	Diff (%)
223 {L. NAC}	75	53.3	21.7
116 {R. A28/34}	57.8	36.7	21.1
224 {R. NAC}	59.4	41.1	18.3
216 {R. rHipp}	60.9	43.3	17.6
212 {R. mAmyg}	67.2	52.2	15.0

Table 5. Ranking of brain region differences at P-score threshold 0.6.

Brain Region	APOE4+	APOE4-	Diff (%)
69 {L. A38m}	60.9	42.2	18.7
220 {R. vCa}	53.1	34.4	18.7
50 {R. A13}	46.9	28.9	18
218 {R. cHipp}	42.2	26.7	15.5
84 {R. A21r}	56.2	42.2	14

Table 6. P-score Thresholds and Identified Key Brain Regions.

Threshold Level	Definition	Key Regions
2.0	Mean + 2.0 × SD	Left Medial Amygdala Right Rostral Area 35/36
1.5	Mean + 1.5 × SD	Right Medial Amygdala Right Nucleus Accumbens
0.6	Mean + 0.6 × SD	Left Superior Temporal Gyrus Right Ventral Caudate

CONCLUSIONS

- ✓ The identified structural vulnerability patterns varied across P-score thresholds, with partial consistency in medial temporal–limbic regions.
- ✓ At the moderate threshold, several regions showed notable group differences between APOE4 carriers and non-carriers.
- ✓ At the more stringent threshold, the left medial amygdala and right rostral area 35/36 emerged as the most prominent regions.

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CONTACT



Dan Pan
1) Guangdong Polytechnic Normal University, Guangzhou 510664, China; pandan@gpnu.edu.cn
2) Department of Psychiatry, School of Clinical Medicine, University of Cambridge, Cambridge CB2 0SP, United Kingdom; dp773@cam.ac.uk

