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ORIGINAL RESEARCH

Distinct neural correlates of episodic memory among apolipoprotein E alleles in cognitively normal elderly

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Abstract

The apolipoprotein E (APOE) ε4 and ε2 alleles are acknowledged genetic factors modulating Alzheimer's disease (AD) risk and episodic memory (EM) deterioration in an opposite manner. Mounting neuroimaging studies describe EM-related brain activity differences among APOE alleles but remain limited in elucidating the underlying mechanism. Here, we hypothesized that the APOE ε2, ε3, and ε4 alleles have distinct EM neural substrates, as a manifestation of degeneracy, underlying their modulations on EM-related brain activity and AD susceptibility. To test the hypothesis, we identified neural correlates of EM function by correlating intrinsic hippocampal functional connectivity networks with neuropsychological EM performances in a voxelwise manner, with 129 cognitively normal elderly subjects (36 ε2 carriers, 44 ε3 homozygotes, and 49 ε4 carriers). We demonstrated significantly different EM neural correlates among the three APOE allele groups. Specifically, in the ε3 homozygotes, positive EM neural correlates were characterized in the Papez circuit regions; in the ε4 carriers, positive EM neural correlates involved the lateral temporal cortex, premotor cortex/sensorimotor cortex/superior parietal lobule, and cuneus; and in the ε2 carriers, negative EM neural correlates appeared in the bilateral frontopolar, posteromedial, and sensorimotor cortex. Further, in the ε4 carriers, the interaction between age and EM function occurred in the temporoparietal junction and prefrontal cortex. Our findings suggest that the underlying mechanism of APOE polymorphism modulations on EM function and AD susceptibility is genetically related to the neural degeneracy of EM function across APOE alleles.

Keywords Apolipoprotein E · Episodic memory · Alzheimer's disease · Aging · Functional connectivity

Introduction

The apolipoprotein E (APOE) gene is a confirmed genetic factor modulating late-onset Alzheimer's disease (AD) risk in an isoform-dependent manner (ε4 > ε3 > ε2) (Corder et al. 1993, 1994). Episodic memory (EM) deficit is the foremost AD symptom at the predementia stage (Dubois et al. 2010). In cognitively normal elderly subjects, the ε4 allele advances EM decline (Caselli et al. 2009; Samieri et al. 2014) while the ε2 allele ameliorates EM loss (Wilson et al. 2002), corresponding to different AD susceptibilities. Disentangling the neural mechanism of the APOE polymorphism effect on EM function could facilitate understanding the nature of APOE polymorphism modulation on AD risk. Various brain EM activity changes in ε4 carriers have been described by functional magnetic resonance imaging (fMRI) studies (Trachtenberg et al. 2012) but remain limited in unraveling the underlying mechanism. For example, depending on whether brain activity contributes to better EM performance,

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the changed brain activity in ε4 carriers may represent a neural trait subserving the ε4 carriers' EM function or a manifestation of neural pathology related to the ε4 allele (Fleisher et al. 2005; Kukolja et al. 2010). It is imperative to move beyond a mere description of brain activity differences among APOE alleles to establish a framework for the underlying mechanism by elucidating neural EM substrates across APOE alleles.

Cognition is believed to arise from functional integration among spatially distributed brain regions (Park and Friston 2013). Particularly, EM function generally relies on a large-scale network that comprises Papez circuit regions (e.g., the hippocampus and thalamus) and neocortical regions including the lateral temporal lobe, lateral prefrontal cortex (LPFC), and anterior medial prefrontal cortex (aMPFC) (Budson and Price 2005; Dickerson and Eichenbaum 2010). However, this EM neural substrate may exhibit dysfunction in mild cognitive impairment (MCI) and AD-type dementia (Sperling et al. 2010; Nellessen et al. 2015), and even in cognitively normal elderly subjects carrying the APOE ε4 allele. Specifically, relative to the ε3 homozygotes, elderly ε4 carriers during EM effort tend to exhibit hypoactivities in regions typically mediating EM function, such as the hippocampus (Suthana et al. 2010; Adamson et al. 2011), and hyperactivities in cortical regions, such as the lateral temporal and frontal cortex, superior parietal lobule, and medial occipital cortex (Bondi et al. 2005; Fleisher et al. 2005; Han et al. 2007; Kukolja et al. 2010). These findings suggest that the brain may recruit a distinct set of brain regions, as a function of APOE polymorphism, to achieve comparable EM performance (Tuminello and Han 2011). Nevertheless, distinct EM neural substrates between the APOE ε3 and ε4 alleles have not yet been demonstrated. Additionally, it is still unknown how the ε2 allele protects against AD at a neural system level, despite abundant biological evidence supporting the ε2 allele's resistance to AD pathogenesis (Suri et al. 2013). Therefore, this study recruited three groups of cognitively normal elderly subjects with different APOE alleles. We hypothesized that the APOE ε2, ε3, and ε4 alleles had distinct EM neural substrates. It required us to relate brain activity to EM function at a brain network level.

An efficient way to localize the brain-behavior relationship is to identify across subjects the brain regions with significant correlations between brain activity and cognitive performance (Rigoux and Daunizeau 2015). Particularly, intrinsic functional connectivity, measured by spatial synchronization of blood-oxygenation-level dependent (BOLD) signal fluctuation, is a potential brain activity indicator, not only in identifying brain networks but also in predicting cognitive performance (Fox and Raichle 2007; Rosenberg et al. 2016). To subserve EM function, the hippocampus acts as a core and necessary node (Tulving and Markowitsch 1998; Budson and Price 2005); the hippocampal functional connectivity (HFC) network provides a neural basis for brain regions responding to EM tasks (Vincent et al. 2006) and could reliably predict neuropsychological EM performance in the posteromedial cortex (Touroutoglou et al. 2015). Therefore, to address our hypothesis, this study will refer to the neural correlates of EM function in the HFC network as the EM neural substrate. Specifically, first, we detected bilateral HFC network differences among groups. Second, a within-group voxelwise linear regression model, between the neuropsychological EM performance and HFC network, identified each group's EM neural correlates; another across-group voxelwise linear regression model examined whether and how the EM neural correlates changed as a function of APOE polymorphism. Finally, aging—another established AD risk factor—was included in the regression models to explore its modulation on each group's EM neural correlates.

Materials and methods

Subjects

Subjects were from the Nanjing Aging and Dementia Study (NADS) dataset described previously (Shu et al. 2016). Briefly, we selected 135 cognitively normal elderly subjects, containing 37 APOE ε2ε3 subjects (abbreviated as "ε2 carriers"), 46 ε3 homozygote subjects, and 52 ε4 carrier subjects, to achieve a comparable sample size among groups. Among these subjects, one APOE ε2 carrier, two ε3 homozygotes, and three ε4 carriers were excluded due to excessive motion artifacts during the fMRI scan (i.e., exceeding 2 mm of maximum displacement in any direction or 2° of angular motion) or incomplete imaging data. The remaining 129 subjects, including 36 APOE ε2 carriers, 44 ε3 homozygotes, and 49 ε4 carriers (including 47 APOE ε3ε4 genotype subjects and two ε4 homozygote subjects), were analyzed further. The Affiliated ZhongDa Hospital of Southeast University Research Ethics Committee approved this study. Written informed consents were obtained individually.

Clinical evaluation

Each subject underwent a standardized clinical inventory including a demographic and medical history inquiry, a physical examination, and APOE genotyping. A battery of multidomain neuropsychological assessments, including general cognition, EM function, visuospatial function, information processing speed, and executive function, also was performed (Shu et al. 2016). Particularly, the EM function tests comprised the Auditory Verbal Learning Test, Logical Memory Test, and Rey-Osterrieth Complex Figure Test (Guo et al. 2009). Each test's 20-min delayed recall score determined the subject's EM function. The EM function assessment and APOE genotyping processes are detailed in supplementary text S1 and S2, respectively.

Inclusion and exclusion criteria

Each subject met the following inclusion criteria: (1) aged between 54 and 80 years; (2) education level above junior high school; (3) right-handed; (4) generally healthy with no disease expected to interfere with cognitive performance; (5) adequate visual and auditory acuity allowing cognitive testing; (6) referring to the Alzheimer's Disease Neuroimaging Initiative (ADNI) criteria, normal general cognition (Mini-Mental State Examination [MMSE] score > 24 and Mattis Dementia Rating Scale-2 [MDRS-2] score > 120) and EM function within age-adjusted normal range (Guo et al. 2009).

The subjects met none of the following exclusion criteria: (1) existence or history of significant neurologic or psychiatric diseases such as stroke, epilepsy, Parkinson's disease, multiple sclerosis, encephalitis, brain tumor, head trauma, craniocerebral operation, schizophrenia, major depression, bipolar disorder, or substance abuse or dependence; (2) Hachinski ischemic score > 4, Hamilton Depression Rating Scale score > 7; (3) current use of psychoactive medications such as neuroleptics, antidepressants, anxiolytics, or other medications with anticholinergic effects in the central nervous system; (4) MRI scan contraindications such as ferrous or electronic implants; (5) evidence of infarction, infection, focal lesions, or gross structural abnormalities in MRI images.

MRI data acquisition

MRI data were acquired using a Siemens Verio 3.0 T (T) scanner (Siemens, Erlangen, Germany) with a 12-channel head coil. The subjects were instructed to relax and close their eyes during the scan. Their ears were occluded with earplugs. A pair of stabilizers minimized the subjects' head motion. Resting-state fMRI (R-fMRI) data, including 240 volumes, were obtained by the gradient-recalled echo-planar imaging (GRE-EPI) sequence: repetition time (TR) = 2000 ms; echo time (TE) = 25 ms; flip angle (FA) = 90°; acquisition matrix = 64 × 64; field of view (FOV) = 240 × 240 mm; thickness = 4.0 mm; gap = 0 mm; number of slices = 36. High-resolution T1-weighted anatomical images were acquired by the 3D magnetization prepared rapid gradient echo (MPRAGE) sequence: TR = 1900 ms; TE = 2.48 ms; FA = 9°; acquisition matrix = 256 × 256; FOV = 250 × 250 mm; thickness = 1.0 mm; gap = 0 mm; number of slices = 176. Additionally, routine axial T2-weighted images were obtained to exclude subjects with major white matter (WM) changes, cerebral infarctions, or other lesions.

fMRI data preprocessing

R-fMRI data were conventionally preprocessed using the Analysis of Functional NeuroImages (AFNI) software (https://afni.nimh.nih.gov/afni) and MATLAB programs (The MathWorks, Inc., Natick, MA, USA). First, the first five volumes of the raw data were discarded to allow for T1 equilibration. Then, time series spikes were removed (3dDespike, AFNI). Correction was performed for the intravolume acquisition time differences among slices and the intervolume motion effects during the scan (3dvolreg, AFNI). Detrending was executed to remove Legendre polynomials (3dDetrend, AFNI). The obtained image was normalized to the Montreal Neurological Institute (MNI) space with a 12-parameter affine approach and an EPI template image, which was then resampled to a $4 \times 4 \times 4$ mm^3 voxel size (Normalise, SPM8). Confounding signals of WM, cerebrospinal fluid (CSF), and six motion vectors were regressed out from voxelwise time series (3dDeconvolve, AFNI). We found no significant motion differences among groups. We calculated the Global Negative Index, the ratio of the number of voxels negatively correlated with the global signal to the total number of voxels, for each subject. All were greater than 3%, suggesting that our data's global signal was irrelevant to nonneural noise and should not be regressed out (Chen et al. 2012). Finally, we applied a bandpass filter to keep low-frequency fluctuations between 0.015 and 0.1 Hz (3dFourier, AFNI).

Hippocampal seed-based functional connectivity analysis

The left and right hippocampus regions of interest (ROIs) were separately extracted from the automated anatomical labeling (AAL) template using the WFU Pickatlas software (Maldjian et al. 2003); then, they were coregistered to the functional data (3dfractionize, AFNI). Next, by averaging the time series of all voxels within the coregistered ROIs, each subject's left and right hippocampal time series were obtained (3dmaskave, AFNI). Voxelwise correlation coefficients (CC) between the seed regions and the whole brain were calculated (3dfim+, AFNI) and then subjected to a Fisher transformation to improve normality [$m = 0.5\ln(1 + CC)/(1\text{-}CC)$] (3dcalc, AFNI). Thus, each subject's left and right HFC networks were obtained, respectively.

Voxelwise gray matter volume correction

The gray matter (GM) volumes were included as covariates in a voxelwise manner to avoid the bias of functional connectivity (FC) strength due to anatomical variation (Bai et al. 2011). All subjects' GM maps were obtained by the voxel-based morphometry 8 (VBM8) toolbox. A study-specific DARTEL template was created to improve the accuracy of the GM volume calculation, according to the VBM8 manual (http://dbm.neuro.uni-jena.de/vbm8/vbm8-manual.pdf). First, all subjects' anatomical images

were segmented into GM and WM; then, they were normalized to the tissue probability maps using an affine registration. Second, these affine-registered GM and WM segments created the study-specific DARTEL template. Third, non-linearly-modulated normalized GM maps were obtained based on the DARTEL template; they were then resampled to the same voxel size as the functional image. Fourth, the resulting GM volume values were regressed out as the nuisance regressor from the FC values in a voxelwise manner across all subjects to control the GM influence on FC strength. Finally, the GM-corrected HFC networks were smoothed with a 6-mm Gaussian kernel (3dmerge, AFNI).

Hippocampal volume analysis

We calculated each subject's left and right hippocampal volumes to investigate whether they were significantly different among the three APOE allele groups. First, the left and right hippocampus ROIs were respectively extracted from the AAL template in the WFU Pickatlas software. Then, each hippocampal ROI was coregistered to the GM and WM volume maps obtained by the VBM8 toolbox. Third, by summating the GM and WM volume values of all voxels within each coregistered ROI, each subject's left and right hippocampal volumes were calculated, respectively. Statistically, one-way analysis of variance (ANOVA) compared hippocampal volumes among groups. We observed no significant differences in the left and right hippocampal volumes among the three APOE allele groups ($p > 0.05$, Table S1).

Statistical analysis

Demographic and neuropsychological data

One-way ANOVA and Chi-squared tests compared quantitative and qualitative variables, respectively. The Tukey–Kramer post hoc test was used if the ANOVA detected significant among-group differences. The statistical significance was set at $p < 0.05$.

Among-group HFC network comparison

Each group's left and right HFC network patterns were obtained using random-effect one-sample *t*-tests (3dttest++, AFNI). One-way analysis of covariance (ANCOVA) compared bilateral HFC networks among groups (3dRegAna, AFNI). Subsequently, post hoc two-sample *t*-tests (3dttest++, AFNI) compared between-group differences of ε4 carrier vs. ε3 homozygous groups, ε2 carrier vs. ε3 homozygous groups, and ε2 carrier vs. ε4 carrier groups. Both ANCOVA and two-sample *t*-tests were controlled for age, gender, family history (FH), and education years. To corrected for multiple comparisons on the statistical maps, we used the 3dFWHMx to estimate the smoothing parameter and 3dClustSim to calculate the cluster size threshold (AFNI version 16.2.06). The statistical threshold was set at $\alpha = 0.01$, determined by voxelwise $p = 0.05$ and cluster size ≥ 7104 mm^3.

Definition of EM performances

To define the EM performances, we transformed raw scores of the three EM tests into one EM composite *Z*-score. First, for each EM test, subjects' raw scores were transformed to *Z*-scores according to Eq. 1

$$Z_i = \left(r_i - \bar{r}\right) / \mathrm{S} \tag{1}$$

where Z_i is the *Z*-score of the *i* th subject, r_i is the raw score of the *i* th subject, $\bar{r}$ is the average raw score for all subjects, and S is the standard deviation of the scores. Second, each subject's EM composite *Z*-score was determined by averaging the *Z*-scores of the three EM tests.

Voxelwise regression with EM function

We applied a within-group voxelwise multivariate linear regression model to identify each group's neural correlates of EM function in the left and right HFC networks, respectively (3dRegAna, AFNI):

$$m_i = \beta_0 + \beta_1 EM + \beta_2 age + \beta_3 edu + \beta_4 gender + \beta_5 FH + \varepsilon \tag{2}$$

In Eq. 2, m_i is the HFC value of the *i*th voxel. β_0 is the intercept of the fitting line. β_1 is the effect of the EM composite *Z*-score. β_2, β_3, β_4, and β_5 are the effects of age, education years, gender, and family history, respectively, as covariates in the model. ϵ denotes random errors. We identified clusters showing significant β_1 as EM neural correlates. Additionally, to validate the obtained EM neural correlates, we employed a bootstrap resampling approach for each region showing significant EM correlation, as detailed in supplementary text S3.

To further investigate whether and how the EM neural correlates change as a function of APOE polymorphism, we employed an across-group voxelwise multivariate linear regression model on the left and right HFC networks, respectively (3dRegAna, AFNI):

$$\begin{aligned} m_i =& \beta_0 + \beta_1 APOE2 + \beta_2 APOE4 + \beta_3 EM + \beta_4 (APOE2 \times EM) \\ &+ \beta_5 (APOE4 \times EM) + \beta_6 age + \beta_7 edu + \beta_8 gender \\ &+ \beta_9 FH + \varepsilon \end{aligned} \tag{3}$$

In Eq. 3, β_1 and β_2 are the effects of APOE status, regarding the ε3 homozygous group as the reference. Specifically,

*APOE*2=1 if the subject carries the ε2 allele; otherwise, *APOE*2=0; *APOE*4=1 if the subject carries the ε4 allele; otherwise, *APOE*4=0. β_3 is the effect of the EM composite *Z*-score. β_4 and β_5 are considered as an entity to represent the interaction between APOE status and the EM composite *Z*-score. β_6, β_7, β_8, and β_9 are the effects of age, education years, gender, and family history, respectively. Implications ofm_i, β_0, and ϵ refer to those in Eq. 2. We identified clusters with significant β_4 and β_5 to detect the EM neural correlates changes among groups.

Voxelwise regression with EM function and age

To further investigate aging modulation on each group's EM neural correlates, we used a within-group voxelwise regression model including the interaction term between EM function and age (3dRegAna, AFNI):

$$m_i = \beta_0 + \beta_1 EM + \beta_2 age + \beta_3 (age \times EM) + \beta_4 edu + \beta_5 gender + \beta_6 FH + \varepsilon \quad (4)$$

In Eq. 4, β_1 and β_2 are the effects of the EM composite *Z*-score and age, respectively. β_3 represents the interaction between age and the EM composite *Z*-score. β_4, β_5, and β_6 are the effects of education years, gender, and family history, respectively. Implications of m_i, β_0, and ϵ refer to those in Eq. 2. To clarify, we have rewritten Eq. 4 below:

$$m_i = \beta_0 + (\beta_1 + \beta_3 age) EM + \beta_2 age + \beta_4 edu + \beta_5 gender + \beta_6 FH + \varepsilon \quad (5)$$

Equation 5 defines the regression coefficient between EM function and HFC strength in the ith voxel as $\beta_1 + \beta_3 age$. The effect of EM function on the ith voxel's HFC strength would depend on age given a statistically significant β_3. Specifically, positive and negative β_3 indicate increased and reduced regression coefficients with advancing age, respectively. We identified clusters showing significant β_3 as aging modulation on the EM neural correlates. In addition, we performed an across-group regression analysis, detailed in supplementary text S4, to detect the difference in aging modulation on the EM neural correlates among the three groups. The statistical thresholds of above voxelwise regression analyses were set at $\alpha = 0.05$, determined by voxelwise $p = 0.05$ and cluster size ≥ 5504 mm^3.

Results

Demographic characteristics and cognitive performances

As shown in Table 1, the three APOE allele groups showed no significant differences in demographic information and cognitive performance except education years ($F = 3.43$, $p = 0.04$). The APOE ε4 carrier group exhibited significantly lower education years relative to the APOE ε2ε3 group (Tukey–Kramer corrected $p < 0.05$).

HFC networks in the three APOE allele groups

Figure 1 shows each group's bilateral HFC network patterns, and Fig. S1 illustrates the APOE polymorphism effects on the bilateral HFC networks that primarily involved the bilateral cuneus. Compared with the ε3 homozygous group, the ε4 carrier group showed increased left (Fig. 2a, b, and Table S2) and right (Fig. S2a, b, and Table S2) HFC networks in the bilateral cuneus/lingual gyrus. Conversely, the ε2 carrier group showed reduced right HFC strength in the bilateral cuneus compared with the ε3 homozygous group (Fig. 2c, d, and Table S2). Additionally, the ε2 carrier group exhibited decreased bilateral HFC networks relative to the ε4 carrier group (Fig. S3).

Distinct EM neural correlates among APOE alleles

We obtained each group's EM neural correlates using the within-group voxelwise regression analysis (Fig. 3 and Table S3). In the ε3 homozygotes, positive EM neural correlates covered the bilateral thalamus and medial temporal lobe (MTL) in the bilateral HFC networks, and also involved the bilateral ventral medial prefrontal cortex (vMPFC)/aMPFC, inferior temporal gyrus, and left LPFC in the right HFC network. Negative EM neural correlates emerged in the bilateral dorsal medial prefrontal cortex (DMPFC)/rostral anterior cingulate cortex (rACC) of the left HFC network. In the ε4 carriers, only positive EM neural correlates were identified in the bilateral cuneus, premotor cortex (PMC)/sensorimotor cortex (SMC)/superior parietal lobule (SPL), and posterior middle temporal gyrus (MTG). Conversely, in the ε2 carriers, only negative EM neural correlates were found in the bilateral frontopolar cortex, posterior cingulate cortex/precuneus, and SMC. The regression coefficients of all of these regions were located within the 95% confidence interval (CI) calculated from the bootstrap resampling approach (Table S3).

EM neural correlates differences among the three APOE alleles were statistically demonstrated by the across-group voxelwise regression analysis (Figs. 4, 5 and 6 and Table S4). Such differences showed distinct neural correlates in the three APOE alleles. In the case of the ε3 homozygotes, both left (Fig. 4a) and right

Table 1 Demographic data and cognitive performance in each group

	APOE ε2ε3 (n = 36)	APOE ε3ε3 (n = 44)	APOE ε4+ (n = 49)	F or $\chi 2$	p
Age (years)	69.33 ± 6.80	68.77 ± 6.62	67.41 ± 6.46	0.98	0.38[a]
Male gender, n (%)	17 (47.2)	23 (52.3)	22 (44.9)	0.52	0.77[b]
Education (years)	13.33 ± 3.00	12.42 ± 3.15	11.60 ± 2.91[d]	3.43	0.04[a,c]
Positive family history, n (%)	4 (11.1)	10 (22.7)	13 (26.5)	3.11	0.21[b]
Hypertension, n (%)	12 (33.3)	19 (43.2)	17 (34.7)	1.04	0.60[b]
Hyperglycemia, n (%)	8 (22.2)	6 (13.6)	11 (22.4)	1.41	0.50[b]
Hyperlipidemia, n (%)	12 (33.3)	10 (22.7)	11 (22.4)	1.58	0.45[b]
Antihypertensive medication, n (%)	12 (33.3)	18 (40.9)	16 (32.7)	0.81	0.67[b]
Antihyperglycemic medication, n (%)	6 (16.7)	3 (6.8)	10 (20.4)	3.56	0.17[b]
Antihyperlipidemic medication, n (%)	4 (11.1)	3 (6.8)	3 (6.1)	0.88	0.71[b]
Antiplatelet medication, n (%)	5 (13.9)	10 (22.7)	8 (16.3)	1.18	0.56[b]
MMSE (raw score)	28.03 ± 1.52	28.57 ± 1.15	28.06 ± 1.55	1.97	0.14[a]
MDRS-2 (raw score)	138.17 ± 4.00	137.86 ± 3.73	137.73 ± 3.20	0.15	0.86[a]
Episodic memory performance					
AVLT–20-min DR (raw score)	7.67 ± 1.90	7.55 ± 1.96	7.49 ± 2.06	0.08	0.92[a]
AVLT–20-min DR (*Z*-score)	0.06 ± 0.96	-0.01 ± 1.00	-0.03 ± 1.05	0.08	0.92[a]
LMT–20-min DR (raw score)	8.04 ± 2.08	8.53 ± 2.63	8.44 ± 2.65	0.42	0.66[a]
LMT–20-min DR (*Z*-score)	-0.13 ± 0.84	0.07 ± 1.06	0.03 ± 1.07	0.42	0.66[a]
CFT–20-min DR (raw score)	19.85 ± 5.44	18.15 ± 6.09	18.36 ± 4.86	1.11	0.33[a]
CFT–20-min DR (*Z*-score)	0.21 ± 1.00	-0.10 ± 1.11	-0.06 ± 0.89	1.11	0.33[a]
Episodic memory composite *Z*-score	0.05 ± 0.67	-0.01 ± 0.78	-0.02 ± 0.67	0.10	0.90[a]

Data are presented as mean ± stand deviation (SD). Subjects from the three APOE allele groups showed no significant differences in demographic information, health status and medication, and general cognitive and episodic memory performance, except education years. *Abbreviations: n* number, *MMSE* Mini-mental state examination, *MDRS-2* Mattis dementia rating scale-2, *AVLT–20-min DR* Auditory verbal learning test–20-min delayed recall, *LMT–20-min DR* Logical memory test–20-min delayed recall, *CFT–20-min DR* Rey-Osterrieth Complex Figure Test–20-min delayed recall

[a] *p* values were obtained by one-way analysis of variance (ANOVA)

[b] *p* values were obtained by Chi-squared tests

[c] Significant difference in education years was found among the three groups

[d] Post hoc tests by Tukey–Kramer analysis demonstrated significant difference between APOE ε4+ and APOE ε2ε3 groups

(Fig. 4b) HFC strengths were positively correlated with EM function in the bilateral thalamus and MTL regions. With regard to the ε4 carriers, positive EM neural correlates involved the bilateral PMC/SMC/SPL in the right HFC network (Fig. 5a, b) and the right MTG in the left HFC network (Fig. 5c). The ε2 carriers demonstrated bilateral HFC strengths that were negatively correlated with EM function in the bilateral frontopolar cortex (Fig. 6).

Aging modulation on the EM neural correlates in the ε4 carriers

The ε4 carriers showed significant aging modulation on the EM neural correlates in the bilateral HFC networks (Figs. 7 and S4 and Table S5). The regression coefficients with EM function related to the bilateral temporoparietal junction (TPJ), right anterior temporal lobe (ATL), and left LPFC in the right HFC network (Fig. 7), as well as the left TPJ in the left HFC network (Fig. S4), were significantly increased with advancing age. Neither the ε2 carriers nor ε3 homozygotes showed such significant aging modulation. The above findings were also supported by the across-group model in demonstrating the difference in aging modulation among groups. Please refer to supplementary text S4 and Fig. S5 for details.

Discussion

The major finding of this study is that the three APOE alleles in cognitively normal elderly subjects had distinct neural correlates of EM function despite having comparable EM performances. Furthermore, we found that aging

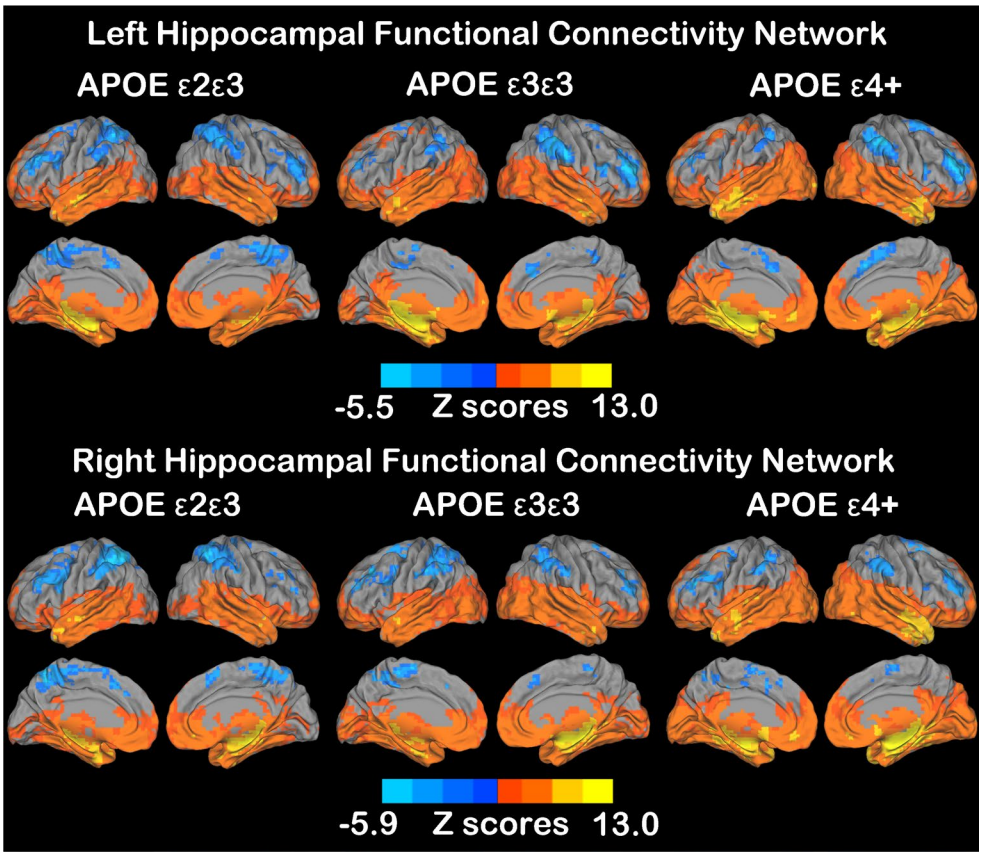

Fig. 1 Whole-brain voxelwise pattern of left (upper panel) and right (lower panel) HFC networks in each APOE allele group. A warm color indicates positive functional connectivity and a cool color indicates negative functional connectivity ($p < 0.05$, AlphaSim correction). The color bar presents Z-scores. Abbreviations: HFC, hippocampal functional connectivity; APOE, apolipoprotein E

can modulate the EM neural correlates in the ε4 carriers. These findings suggest that the neural degeneracy of EM function across APOE alleles may underlie the APOE polymorphism effects on brain activity and AD susceptibility.

Our findings with regard to EM neural correlates in the ε3 homozygotes are consistent with the acknowledged EM circuit at the neural system level. For example, the positive EM neural correlates in the bilateral MTL and thalamus are parts of the Papez circuit, which is an established key substrate for learning and memory (Vertes et al. 2001). The prefrontal regions (bilateral vMPFC/aMPFC and left LPFC) in the positive EM neural correlates also subserve EM function (Budson and Price 2005). Specifically, the LPFC advances the selection of goal-relevant information and organization of among-material associations during EM encoding (Blumenfeld and Ranganath 2007), and the vMPFC/aMPFC supports EM retrieval (Dickerson and Eichenbaum 2010). It has been proposed that the LPFC, vMPFC, MTL, and thalamus are reciprocally interconnected as a thalamo-prefrontal network to subserve goal-directed EM formation (Pergola and Suchan 2013). Our results corroborate this view by demonstrating the association of better EM performance with greater functional integration between the prefrontal and Papez circuit regions. In addition, the negative EM neural correlates in the bilateral DMPFC and rACC may indicate social cognitive interference in EM effort (Etkin et al. 2011). Accordingly, these neural correlates of EM function are justified as EM neural substrates in the ε3 homozygotes.

With reference to the APOE ε3 homozygotes' EM neural correlates, we demonstrated modulations of the ε4 and ε2 alleles on the EM neural correlates, respectively. Specifically, the ε4 carriers' EM neural correlates, characterized in the PMC/SMC/SPL, lateral temporal cortex, and medial occipital cortex were positive, while the ε2 carriers' EM neural correlates, involving the posteromedial, sensorimotor, and frontopolar cortex, were negative. These results indicate distinct EM neural substrates among the three APOE alleles. This many-to-one structure–function relationship, which denotes spatially different sets of brain regions to perform the same function, is defined as the degeneracy of brain network organization (Edelman and Gally 2001; Noppeney et al. 2004). Generally, degeneracy is a ubiquitous and prerequisite property of various biological systems, from genetic code to behavioral repertoires, in advancing natural selection and biological

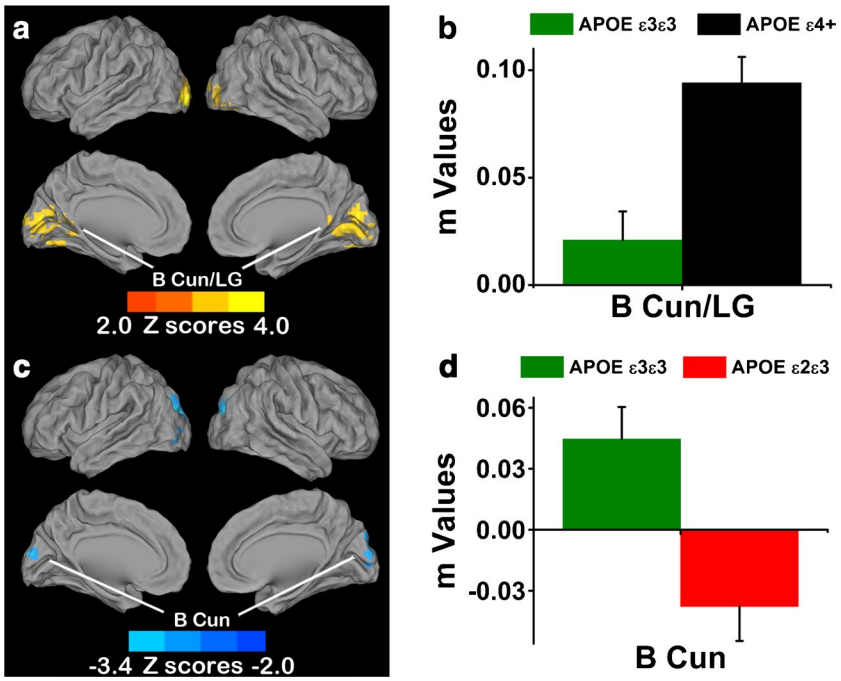

Fig. 2 Altered HFC networks in the APOE ε4 and ε2 carrier groups compared with the APOE ε3 homozygous group. a and **b**, with regard to the APOE ε4 carrier group, significantly increased left HFC network was observed in the bilateral cuneus/lingual gyrus (**a**) compared with the APOE ε3 homozygous group ($p < 0.05$, AlphaSim correction). The color bar presents *Z*-scores. The increased left HFC network shown in **a** is numerically represented in **b**. The m value is the Fisher-transformed correlation coefficient. The error bars represent standard error of the mean. **c** and **d**, with respect to the APOE ε2 carrier group, significantly decreased right HFC network was observed in the bilateral cuneus (**c**) compared with the APOE ε3 homozygous group. The decreased right HFC network shown in **c** is numerically represented in **d**. Abbreviations: B Cun/LG, bilateral cuneus/lingual gyrus; B Cun, bilateral cuneus; Zmemory, episodic memory composite *Z*-score; HFC, hippocampal functional connectivity; EM, episodic memory; APOE, apolipoprotein E

evolution (Edelman and Gally 2001). Herein, distinct sets of brain regions emerge in a degeneracy manner to maintain EM function among different APOE alleles. This agrees with one of the degeneracy manifestations in which the brain's functional network reorganizes in response to genetic variability at an intersubject level (Noppeney et al. 2004). Therefore, the distinct EM neural correlates among APOE alleles reflect the degeneracy of EM function at the brain network level.

Degeneracy provides a general, fundamental framework to understand APOE polymorphism effects on the brain's structural relationship with EM function. Converging studies suggest that APOE ε3 homozygotes and ε4 carriers perform EM function in distinct ways (Tuminello and Han 2011). Specifically, in the ε3 homozygotes, the MTL region is activated during EM tasks; greater MTL activation correlates with better EM performance (Fleisher et al. 2005; Kukolja et al. 2010). By contrast, in the ε4 carriers, such a brain structure–function relationship did not emerge; their brain activation map lies beyond the acknowledged Papez circuit regions including the PMC/SMC/SPL, lateral temporal cortex, and medial occipital cortex (Kukolja et al. 2010; Han et al. 2007; Bondi et al. 2005; Fleisher et al. 2005), which correspond with the ε4 carriers' EM neural correlates observed in this study. Particularly, this study identified the premotor and sensorimotor cortex as the distinct EM neural correlates in the ε4 carriers. Recently, motor dysfunction is indicated as an early pathophysiological event to detect AD and advance the disease development (Albers et al. 2015; Laske et al. 2015). For example, gait dysfunction precedes (Buracchio et al. 2010; Mielke et al. 2013) and predicts (Verghese et al. 2007; Marquis et al. 2002) incidents of MCI and dementia. Greater gait dysfunction at the preclinical stage is associated with the presence of the APOE ε4 allele (Buchman et al. 2009; Melzer et al. 2005) and higher Aβ deposition in regions mediating gait control, such as the SMC (Nadkarni et al. 2017). These studies corroborate our findings that the distinct EM neural correlates in the motor-related cortex may be associated with increased AD susceptibility in the ε4 carriers.

The negative EM neural correlates in the ε2 carriers also contribute to the degeneracy of EM function. Relative to abundant studies focusing on the ε4

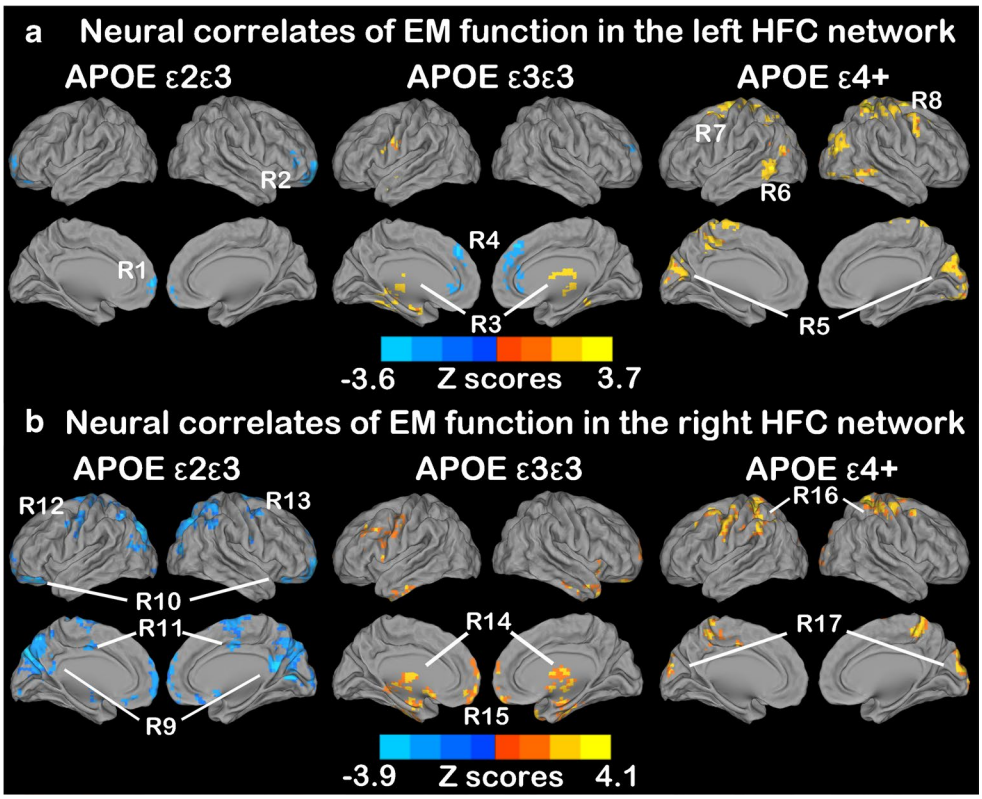

Fig. 3 Neural correlates of EM function in the left (a) and right (b) HFC networks from the three APOE allele groups. A warm color indicates positive HFC correlation with EM function, while a cool color denotes negative HFC correlation with EM function. The color bar presents *Z*-scores. Abbreviations: R1, left frontopolar cortex; R2, right frontopolar cortex; R3, bilateral thalamus/left medial temporal lobe; R4, bilateral dorsal medial prefrontal cortex/rostral anterior cingulate cortex; R5, bilateral cuneus/right middle temporal gyrus; R6, left posterior middle temporal gyrus; R7, left premotor cortex/sensorimotor cortex/superior parietal lobule; R8, right premotor cortex/sensorimotor cortex/superior parietal lobule; R9, bilateral posterior cingulate cortex/precuneus; R10, bilateral frontopolar cortex; R11, bilateral paracentral lobule; R12, left precentral gyrus; R13, right premotor cortex; R14, bilateral thalamus/medial temporal lobe/inferior temporal gyrus/left lateral prefrontal cortex; R15, bilateral ventral/anterior medial prefrontal cortex; R16, bilateral premotor cortex/sensorimotor cortex/superior parietal lobule; R17, bilateral cuneus; HFC, hippocampal functional connectivity; EM, episodic memory; APOE, apolipoprotein E

allele, the mechanism of the ε2 allele protecting against AD receives much less attention (Suri et al. 2013). Herein, the negative EM neural correlates indicate that decreased connectivity strength with the hippocampus promotes EM performance in the ε2 carriers. It may parallel current literature in which the ε2 allele's protective effect is associated with its decreased neural activity. Specifically, the elderly ε2 carrier cohort is suggested to exhibit decreased brain EM activity (Nichols et al. 2012) and reduced long-term potentiation (LTP) activity (Conejero-Goldberg et al. 2014). These observations are corroborated by a rodent study in which the apoE2 protein would attenuate an aberrant increase in LTP activity related to the apoE4 protein (Korwek et al. 2009). In addition, decreasing neural activity by antiseptic treatment shows a protective effect by reversing synaptic and memory deficits in AD (Sanchez et al. 2012). Accordingly, our finding regarding the negative neural correlates adds evidence to the developing understanding of the APOE ε2 allele's effect on brain EM activity, and may account for decreased AD susceptibilities related to the ε2 allele.

Degeneracy manifests not only in distinct EM neural correlates among the three APOE alleles, but also in aging modulation on the EM neural correlates in the ε4 carriers. The age-related elevated regression coefficients between EM performance and HFC strengths in the bilateral TPJ, right ATL, and left LPFC indicate that the ε4 carriers increasingly recruit these brain regions with advancing age to perform EM function. Interestingly, this recruitment pattern appears spatially analogous with the AD signature regions (Dickerson et al. 2009). Cortical thinning in AD signature regions is evident and associated with cognitive deficit severity in AD patients (Dickerson et al. 2009). In

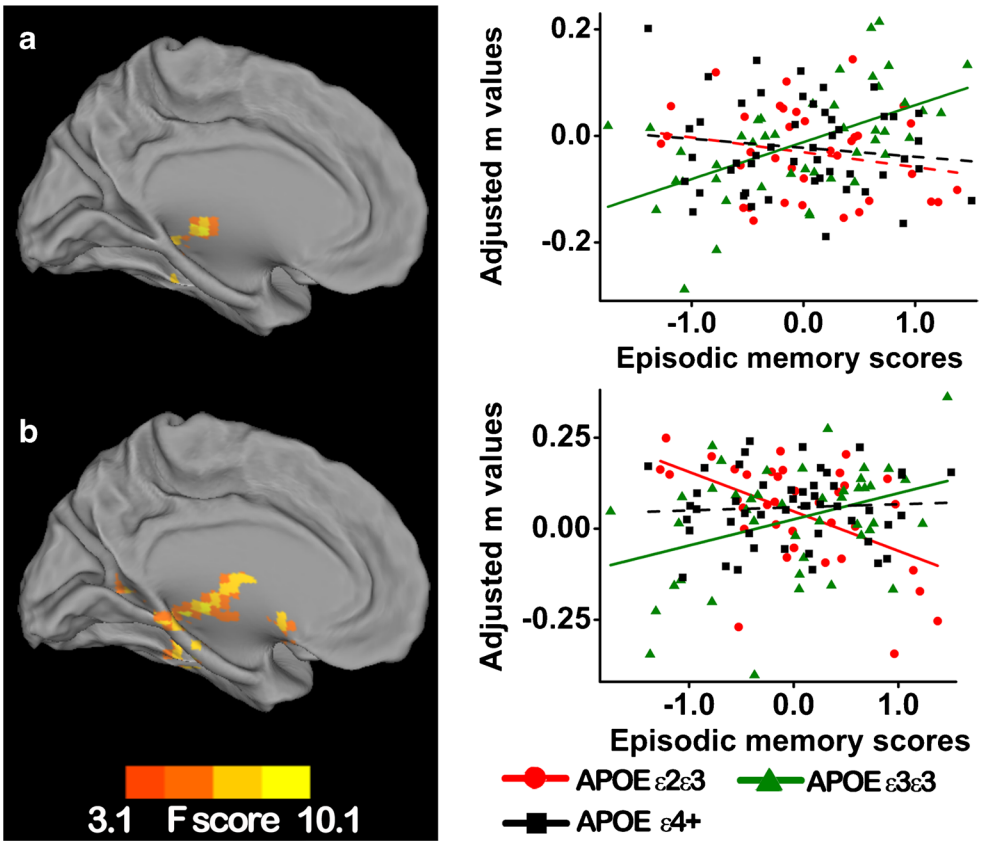

Fig. 4 Differences of EM neural correlates among the three APOE allele groups in the Papez circuit regions. Left panel: brain regions within the Papez circuit show significant interactions between APOE status and EM score on the left (**a**) and right (**b**) HFC network. In these regions, the regression coefficients between HFC strength and EM performance were different among the three APOE allele groups. The color bar presents F scores. Right panel: numerical representations depict different relationships between the HFC strengths and EM scores among the three APOE allele groups in the corresponding regions of the left panel. The solid lines indicate statistically significant within-group correlations; the dashed lines denote statistically nonsignificant within-group correlations (same for Figs. 5 and 6). **a**, significantly positive correlation between the left HFC and EM performance was observed in the ε3 homozygotes (green line), while this relationship was found in neither ε4 (black line) nor ε2 carriers (red line). **b**, positive correlation between the right HFC strength and EM performance was also found in the ε3 homozygotes (green line). By contrast, the ε2 carriers exhibited a negative correlation (red line), and the right HFC strength in the ε4 carriers was irrelevant to EM performance (black line). Abbreviations: HFC, hippocampal functional connectivity; EM, episodic memory; APOE, apolipoprotein E

nondemented elderly subjects, cortical thinning in AD signature regions is associated with a lower CSF Aβ level (Dickerson et al. 2012) and aberrant hippocampal hyperactivity (Putcha et al. 2011), and predicts subsequent cognitive deterioration (Dickerson et al. 2011; Bakkour et al. 2009), thereby serving as a potential early AD biomarker. Therefore, our results imply that a spatial similarity between distinct EM neural correlates and AD signature regions in the older ε4 carriers may underlie their increased risk for cognitive deterioration.

In addition, this study demonstrated that HFC in the cuneus increased and decreased in the ε4 and ε2 carriers, respectively, relative to the ε3 homozygotes. Several lines of evidence indicate that the cuneus is affected early in the AD spectrum. First, AD pathologies emerge in the cuneus in more than half of the cognitively normal subjects and in all MCI and dementia subjects, even without substantial pathology in the MTL (McKee et al. 2006). Second, aberrant metabolism in the cuneus could predict MCI conversion to dementia with high accuracy (Modrego et al. 2005). Third, the cuneus may be an important region for APOE-driven difference in the brain (Dowell et al. 2016). The APOE ε4 allele is not only related to cuneus atrophy in a normal elderly cohort (Yokoyama et al. 2015), it also increases synchronization of the default mode network with the hippocampus and cuneus in a middle-aged cohort (Westlye et al. 2011). Therefore, the altered HFC network in the cuneus found herein is in line with the above studies regarding the early involvement of the cuneus in AD development.

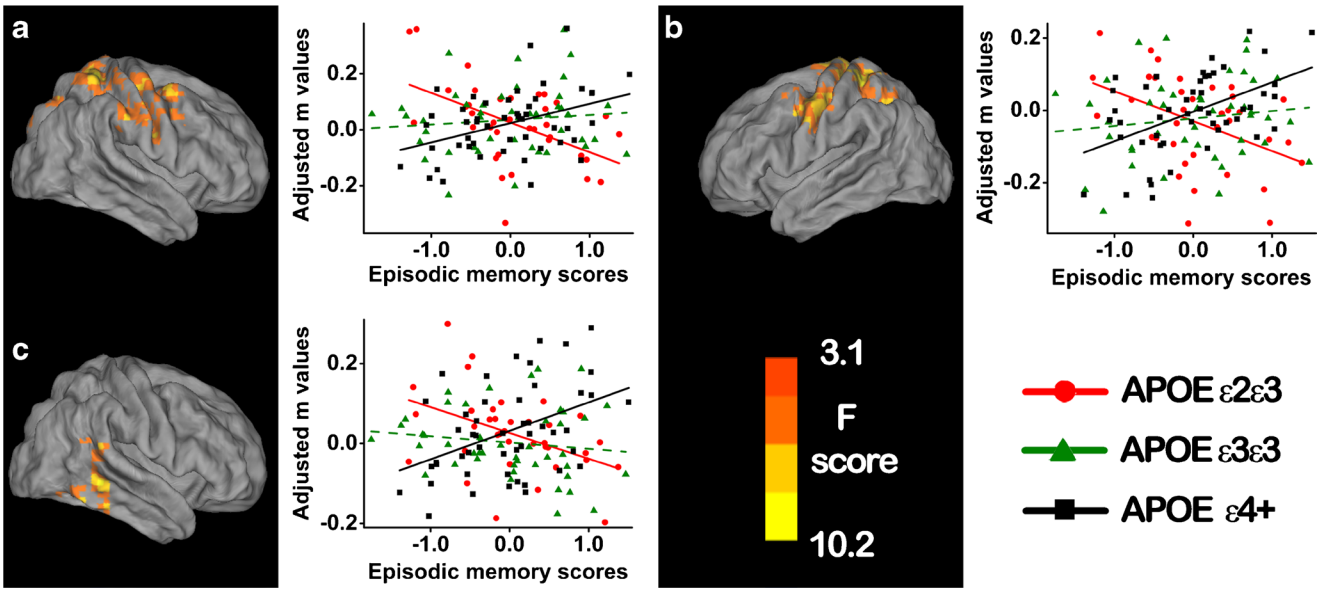

Fig. 5 Differences of EM neural correlates among the three APOE allele groups in the sensorimotor and temporal regions. **a** and **b**, the regression coefficients between the right HFC strength and EM performance in the right (**a**) and left (**b**) premotor cortex/sensorimotor cortex/superior parietal lobule were different among the three APOE allele groups. **c**, the regression coefficients between the left HFC strength and EM performance in the right middle temporal gyrus were dissimilar among the three APOE allele groups. The color bar presents F scores. In all three regions, the ε4 carriers showed positive correlations between HFC strengths and EM performances (black lines), while the ε2 carriers exhibited negative correlations (red lines) and the ε3 homozygotes showed no significant correlation (green lines). Abbreviations: HFC, hippocampal functional connectivity; EM, episodic memory; APOE, apolipoprotein E

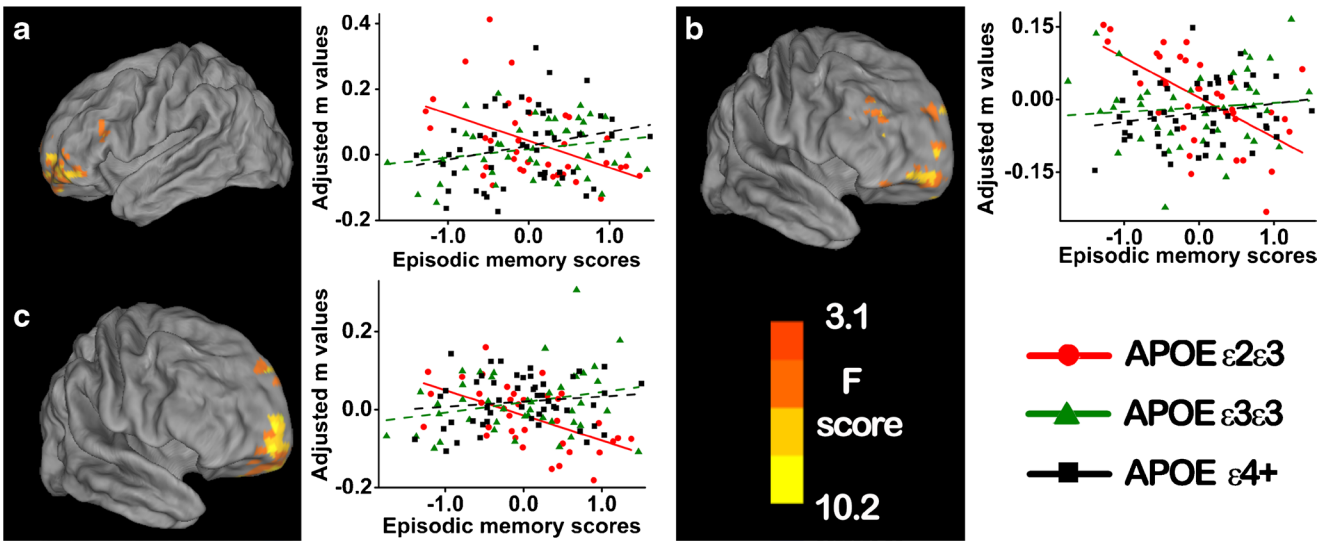

Fig. 6 Differences of EM neural correlates among the three APOE allele groups in the frontopolar cortex. **a** and **b**, the regression coefficients between the left HFC strengths and EM performances in the left (**a**) and right (**b**) frontopolar cortex were different among the three APOE allele groups. **c**, the regression coefficients between the right HFC strengths and EM performances in the frontopolar cortex were dissimilar among the three APOE allele groups. The color bar presents F scores. In all three regions, the ε2 carriers showed significantly negative correlations between the HFC strengths and EM performances (red lines), while no significant correlation was observed in the ε4 carriers (black lines) or ε3 homozygotes (green lines). Abbreviations: HFC, hippocampal functional connectivity; EM, episodic memory; APOE, apolipoprotein E

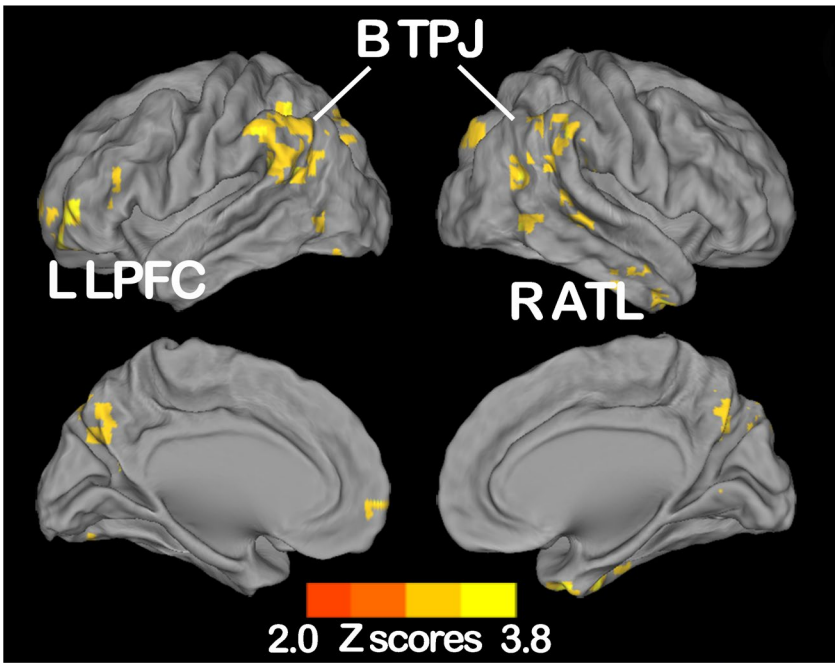

Fig. 7 Aging modulation on the APOE ε4 carriers' EM neural correlates in the right HFC network. Brain regions in warm colors indicate that the regression coefficients between the right HFC strengths and EM performances significantly increased with advancing age. The color bar presents *Z*-scores. Abbreviations: B TPJ, bilateral temporoparietal junction; L LPFC, left lateral prefrontal cortex; R ATL, right anterior temporal lobe; HFC, hippocampal functional connectivity; APOE, apolipoprotein E; EM, episodic memory

Whether this alteration is related to the different AD risks among APOE alleles remains to be demonstrated in future studies.

This study is an initial exploration into the degeneracy of the EM neural substrate across APOE alleles and has certain limitations, discussed below. First, the linear correlation model remains limited in revealing all regions participating in EM production and in uncovering the nature of neural information processing to perform EM function (Valdes-Sosa et al. 2011). Second, degeneracy accompanies network complexity and, thus, needs to be measured by topological modeling metrics at a whole-brain-network level (Mason et al. 2015). Topological analysis may estimate degeneracy levels and network robustness across APOE alleles. Third, a longitudinal study is essential to demonstrate the contribution of the degeneracy to different AD susceptibilities among the APOE alleles. Therefore, further studies with other biophysical models, topological analyses, or a longitudinal study design are necessary to characterize the degeneracy of EM neural substrates and evaluate its relation to cognitive deterioration in subjects with different APOE alleles.

In summary, this study demonstrates that the EM neural correlates in cognitively normal elderly cohorts are not identical but exhibit distinction in response to APOE polymorphism. These findings suggest a degeneracy framework as an underlying mechanism to understand the APOE polymorphism modulations on brain EM activity and susceptibility to AD. Further works are essential to developing the framework, through quantitative measurement of degeneracy from a complex network perspective and determination of degeneracy's role in promoting differential AD hazards among the three APOE alleles. Altogether, degeneracy provides a novel and potential window to investigate the mechanism of brain function variance among different APOE alleles at a neural system level.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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