Default Mode Network Connectivity Moderates the Relationship Between the *APOE* Genotype and Cognition and Individualizes Identification Across the Alzheimer's Disease Spectrum

Yao Zhu, Liang Gong, Cancan He, Qing Wang, Qingguo Ren* and Chunming Xie*
on behalf of Alzheimer's Disease Neuroimaging Initiative[1]
Department of Neurology, Affiliated ZhongDa Hospital, School of Medicine, Southeast University, Nanjing, Jiangsu, China

Abstract. Although previous studies have investigated the effects of the apolipoprotein E (*APOE*) $\varepsilon 4$ genotype on the default mode network (DMN) in the Alzheimer's disease (AD) spectrum, it is still unclear how the *APOE* genotype regulates the DMN and subsequently affects cognitive decline in the AD spectrum. One hundred sixty-nine subjects with resting-state functional magnetic resonance imaging data and neuropsychological test scores were selected from the Alzheimer's Disease Neuroimaging Initiative. The main effects and interaction of the *APOE* genotype and disease status on the DMN were explored. A moderation analysis was performed to investigate the relationship among the *APOE* genotype, DMN connectivity, and cognition. Additionally, the pair-wised DMN connectivity was used to classify AD spectrum, and the classification accuracy was validated. Compared to *APOE* $\varepsilon 4$ non-carriers, *APOE* $\varepsilon 4$ carriers showed the opposite trajectory of DMN connectivity across the AD spectrum. Specifically, the strengths in the posterior cingulate cortex (PCC) connecting with the right precuneus, insular, and fusiform area (FFA) were positively correlated with Mini-Mental State Examination (MMSE) scores in *APOE* $\varepsilon 4$ non-carriers but not in *APOE* $\varepsilon 4$ carriers. Furthermore, PCC-right FFA connectivity could moderate the effects of the *APOE* genotype on MMSE scores across the disease groups. More importantly, using a receiver operating characteristic analysis, these altered connectivities yielded strong classification powers in a pathological stage-dependent manner in the AD spectrum. These findings first identified the intrinsic DMN connectivity moderating the effect of the *APOE* genotype on cognition and provided a pathological stage-dependent neuroimaging biomarker for early differentiation of the AD spectrum.

Keywords: Alzheimer's disease, apolipoprotein E, classification, moderation analysis, resting-state functional magnetic resonance imaging

---

*Correspondence to: Qingguo Ren and Chunming Xie, Department of Neurology, Affiliated ZhongDa Hospital, School of Medicine, Southeast University, Nanjing, Jiangsu 210009, China. Tel.: 0086 25 83262241; E-mails: 10101 1769@seu.edu.cn (Chunming Xie); 101011331@seu.edu.cn (Qingguo Ren).

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a severe cognitive impairment in the elderly. Most new pharmacotherapies in clinical trials to treat AD have failed and have indicated that the time window for AD treatment should be in advance of symptoms occurring in patients with AD. In fact, substantial progress has been made in revealing the pathogenesis of AD, and research interest has moved toward the early stages, including the prodromal and even preclinical stage of AD [1, 2]. The National Institute on Aging–Alzheimer's Association (NIA–AA) research framework defines AD as a biological process that spans from normal to dementia [3]. Amyloid-β (Aβ) accumulation may begin decades before dementia, and there is already substantial neuronal loss by the early stages of AD [4, 5]. While it is important to encourage of lifestyle modifications and allow medical management at the early stages of AD, disease-modifying treatment that halts or slows progression of the disease remains the ultimate goal. Prevention of dementia by targeting modifiable risk factors and neural reserve capacity could be more cost-effective and efficacious [6, 7]. Mild cognitive impairment (MCI), especially amnestic MCI (aMCI), is more likely to develop into AD, particularly if it displays biomarker evidence of AD [8, 9]. So far, accumulating evidence has divided MCI stages into early MCI (EMCI) and late MCI (LMCI) based on the severity of delayed memory impairment in logical memory, which is often used to detect the characteristics of cognitive decline across the AD spectrum [10–12]. Recently, neuroimaging studies have been widely applied and obtained fruitful findings for understanding the AD spectrum. For example, the default mode network (DMN), including the posterior cingulate cortex (PCC), precuneus, medial prefrontal cortex, inferior parietal lobule, lateral temporal cortices, and hippocampus in structure, is necessary for functional cognitive processing [13–15]. Disrupted connectivity in the DMN is associated with amyloid accumulation and closely linked with the pathology of AD [16]. More recently, abnormal DMN subnetworks have also been reported and suggest that the distinct role of the DMN subsystem with special functional-anatomic connectivity is involved in the pathophysiological profiles of the AD spectrum [17–19]. Also important is the suggestion that the posterior DMN, especially for the PCC as a key hub, could initiate connectivity-based cascading network failures during the AD spectrum

[20, 21]. These findings strongly indicate that the DMN may potentially be a biomarker for predicting AD progression. However, little is known about which connectivity within the DMN could predict progression of the AD spectrum. Therefore, the first goal of current study is to investigate the distinct connectivity within the DMN that could represent the progressive biomarker across the AD spectrum.

Hypotheses about the molecular mechanisms of AD includes amyloid cascade, tau pathology, lipid metabolism, innate immunity, inflammation, and endocytosis. One hypothesis of the pathogenic role of apolipoprotein E (*APOE*) ε4 in AD is associated with the reduction of Aβ clearance and cholesterol transport, leading to Aβ aggregation, and subsequently increasing neuronal atrophy and synapse loss [22–24]. The *APOE* ε4 genotype is a major risk factor for developing AD. *APOE* ε4 carriers demonstrate hippocampal atrophy and more damage to episodic memory than *APOE* ε4 non-carriers [25–28]. *APOE* ε4 carriers also show decreased effective connectivity, which reflects the direct causal effects between the PCC and middle temporal gyrus, anterior cingulate cortex, and precuneus in the cognitively intact elderly [29]. Our previous study identified that less disrupted DMN connection in *APOE* ε4 carriers was significantly associated with better episodic memory scores in middle-aged adults [30], and that *APOE* ε4 carriers represented opposite aging trajectories of the DMN in elderly adults [31]. Furthermore, in aMCI patients with *APOE* ε4, the anterior DMN connectivity partially negatively mediates the association between posterior DMN connectivity and episodic memory, and the posterior DMN connectivity also partially negatively mediates the association between anterior DMN connectivity and episodic memory [32]. In addition, Mckenna et al. [33] demonstrated that *APOE* ε4 carriers disrupted the networkcharacteristics of the DMN in EMCI compared to normal aging subjects. Taken together, the *APOE* ε4 genotype is associated with impaired connectivity within the DMN and a cognitive decline in the AD spectrum. However, abnormal connectivity within the DMN and how to moderate the effects of the *APOE* genotypes on cognitive function has rarely been investigated, and, more importantly, how this abnormal connectivity based on the *APOE* genotype could classify AD spectrum subjects still remains unknown. The specific objectives of this study, therefore, were to identify the main effects and interaction of the *APOE* genotype and disease status on the DMN by using the resting-state functionalmagneticresonance(rs-fMRI)

approach in the AD spectrum. A moderation analysis was employed to investigate whether the intrinsic DMN connectivity moderates the effects of the *APOE* genotype on cognitive function across the disease groups. Finally, the altered connectivity within the DMN based on the *APOE* genotype was also used to classify AD spectrum subjects, and a disease stage-dependent neuroimaging biomarker for the early differentiation of AD spectrum was obtained.

MATERIALS AND METHODS

ADNI database and participants

All data were obtained from the ADNI database (http://adni.loni.usc.edu). The rs-fMRI scans images were baseline enrolment from ADNI-1, ADNI-GO, and ADNI-2. If two rs-fMRI studies were performed on the same day, the first scan was chosen unless it did not meet ADNI rs-fMRI protocol standards or quality control measures. We defined the first available scan for each subject as the baseline scan to be included in this analysis ($n = 182$ unique baseline scans). Brain lesion ($n = 2$), uncertain clinical diagnosis ($n = 2$), and structural image quality control failure ($n = 1$) were excluded. Eight subjects (2 CN, 2 EMCI, 3 LMCI, and 1 AD) were excluded due to excessive motion (see data preprocessing). *APOE* genotyping for all participants was performed as previously described [34]. In brief, genomic DNA was extracted from peripheral blood cells. The cells were collected in single EDTA plastic tubes (10 ml) and were sent to the University of Pennsylvania AD Biofluid Bank Laboratory. More detailed information was available in the ADNI-1 Procedures manual. A total of 169 subjects were enrolled in the current study, including 46 cognitive normal (CN), 52 EMCI, 41 LMCI, and 30 patients with AD (Supplementary Fig. 1). Individuals with one or more *APOE* ε4 alleles were classified as *APOE* ε4 carriers (*APOE* ε4+), while subjects with no *APOE* ε4 alleles were classified as *APOE* ε4 non-carriers (*APOE* ε4–). According to the ADNI protocol, the CN subject were verified as free of memory complaints, beyond what one would expect for age. EMCI, LMCI, and AD subjects had a subjective memory concern as reported by the subject, study partner or clinician. The EMCI and LMCI subjects' Mini-Mental State Examination (MMSE) scores were between 24 and 30, Clinical Dementia Rating (CDR) scores of 0.5. while the AD subjects' MMSE scores were between 20 and 26, CDR scores of either 0.5 or 1.0 and meet the NINCDS/ADRDA

criteria for probable AD [35]. To distinguish between EMCI and LMCI, abnormal memory function was documented by scoring the Logical Memory II sub-scale (Delayed Paragraph Recall) from the Wechsler Memory Scale-Revised after the education adjusted ranges: EMCI: a) 9–11 for 16 or more years of education; b) 5–9 for 8–15 years of education; c) 3–6 for 0–7 years of education; LMCI: a) ≤8 for 16 or more years of education; b) ≤4 for 8–15 years of education; c) ≤2 for 0–7 years of education. The functional brain MRI data and corresponding clinical data were downloaded before November 24, 2017 from the publicly available ADNI database. All the detailed description of the neuropsychological measure was presented in the Supplementary Material.

Data acquisition

All subjects were scanned on a 3.0-Tesla Philips MRI scanner. rs-fMRI images were obtained using an echo-planar imaging sequence with the following parameters: 140 time points, repetition time (TR) = 3000 ms, echo time (TE) = 30 ms, flip angle = 80°, number of slices = 48, slice thickness = 3.3 mm, spatial resolution = $3 \times 3 \times 3$ mm^3, acquisition matrix = 64×64, and field of view (FOV) = 240×240 mm. All original image files were available to the general scientific community. T1-weighted images were acquired using a sagittal magnetization prepared rapid gradient echo (MP-RAGE), with data parameters: TR = 6700 ms, TE = 3.1 ms, slice thickness = 1.2 mm, FA = 9° FOV = 250×250 mm, thickness = 1.0 mm, gap = 0 mm, and number of slices = 170.

Data preprocessing

The data preprocessing was performed using the Data Processing Assistant for a Resting-State fMRI (DPARSF, http://www.restfmri.net), which is based on Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm) and the rs-fMRI Data Analysis Toolkit (REST, http://www.restfmri.net). Data analyses of the groups were conducted with the SPM8 toolkit. Briefly, the first 10 volumes of the scanning session were discarded to allow for T1 equilibration effects. The remaining images were corrected for timing differences and motion effects. No translation or rotation parameters of head motion in any given data set exceeded ± 3 mm or ± 3°. The resulting images were spatially normalized to the standard Montreal

Neurological Institute (MNI) echo-planar imaging template using the default settings, resampling to $3 \times 3 \times 3 \, mm^3$ voxels, and smoothed with a Gaussian kernel of $6 \times 6 \times 6 \, mm$. To further reduce the effects of confounding factors, 6 head motion parameters, as well as global mean signal, white matter signal, and cerebrospinal fluid (CSF) signal, was removed from the data through linear regression. Finally, a bandpass filter was applied to keep only low-frequency fluctuations between 0.01–0.08 Hz.

Voxel-wised DMN functional connectivity (FC) analysis

6 mm-radius sphere centered at the PCC (MNI space, coordination is (0, –53, 26)) served as the seed region [36, 37]. For each subject, the mean time series of the seed region was computed as the reference time course. Then, a Pearson cross-correlation analysis was performed between the seed time course and the time course of the whole-brain voxels. Next, a Fisher's z-transformation was applied to improve the normality of the correlation coefficients $[m = 0.5\ln(1 + r)/(1–r)]$. In this way, individual DMN FC map was obtained.

Structural image analysis

To avoid the bias of functional connectivity strength due to anatomical variation, the gray matter (GM) volume was considered as an important covariate in the functional connectivity analysis [38, 39]. An optimized voxel-based morphometry analysis was performed using the VBM8 toolbox in SPM8 to calculate the GM volume in all subjects. In brief, the T1-weighted images were segmented to GM, white matter, and CSF, and then the segmented GM was normalized and smoothed as the functional image. The final images were regressed out as covariate of no interest to control the effect of GM volumes on the intrinsic functional connectivity strength.

Statistical analysis

Demographic information and neuropsychological performance

Analysis of variance (ANOVA) and chi-square tests (applied for the comparisons of gender) were used to compare the demographic data. Mixed analysis of covariance (ANCOVA), with the disease and genes as fixed factors, was used to analyze the neuropsychological performances among subjects with

statistically significant differences ($p < 0.05$) after controlling for age, gender, and education, followed by a *post hoc* test to determine the significance of the specific comparisons ($p < 0.05/3 = 0.017$, Bonferroni correction). All statistical procedures utilized SPSS 19.0 software (SPSS, Inc., Chicago, IL, USA).

Group-level intrinsic DMN connectivity analysis

To analyze the main effect and interaction between the *APOE* genotype and disease status on the DMN, a whole-brain voxel-wised ANCOVA was performed with the *APOE* genotype (ε4 carriers and non-carriers) and the disease status (CN, EMCI, LMC, or AD) as the fixed factors after controlling the effects of age, gender, education, and GM volumes. The thresholds were set at $p < 0.001$, which was determined by Monte Carlo simulation for multiple comparisons after being corrected with the latest 3dClustSim program (cluster level $\alpha < 0.05$, https://afni.nimh.nih.gov/pub/dist/doc/program_help/ 3dClustSim.html, cluster size ≥ 30voxels). All the results were projected onto the surface brain template. To quantitatively represent these altered DMN, the averaged m-values (correlation coefficients after Fisher z transformation) in each target region was extracted from the individual DMN and shown with histograms using REST 1.8.

Behavioral significance

To investigate the behavioral significance of the altered DMN connectivity, a linear regression analysis was employed as below [40, 41]:

$$MMSE = \beta 0 + \beta 1^*mi + \beta 2^*Age + \beta 3^*Gen + \beta 4^*Edu + \beta 5^*GM + \varepsilon$$

where mi is the m value of the ith region of the altered DMN from the main effects and interaction of the *APOE* genotype and disease status across the disease groups, $\beta 0$ is the intercept of the straight line fitting in the model, and $\beta 1$ is the effect of functional connectivity strength of the ith region within the DMN on the MMSE scores. $\beta 2$, $\beta 3$, $\beta 4$, and $\beta 5$ are the effects of age, gender, education, and GM atrophy, respectively, as covariances of no interest in the linear regression model.

Mediation and moderation analysis

In this study, the MMSE was included as part of the diagnostic pathway for disease groups and a common comparator for the principal test assessed. To explore the potential relationships among the *APOE*,

the intrinsic DMN FC, and behavior (MMSE), as well as to further examine whether the DMN FC strength could mediate the effects of the *APOE* genotype on the MMSE across the disease groups, a mediation analysis was performed. This analysis was selected from PROCESS Marco in the SPSS for the mediation analysis (model 4) [42].

A moderation analysis was used to address whether an effect exists and, if so, when, under what circumstances and in what magnitude such effect exists. A simple linear moderation model from PROCESS Marco in SPSS for the moderation analysis (model 1) was employed [43]:

$$Y = iy + b1\,X + b2W + b3XW$$

where X represents the independent variable (*APOE* genotype), Y represents the dependent variable (MMSE), and W represents the moderator, which was measured by the DMN FC strength in each region of interest (ROI) from the interactive effect of the *APOE* genotype and disease status. X's effect on Y is also said to be moderated by W if the size or sign of X's effect on Y varies with W. If b3 is different than zero, this means that X's effect on Y varies with W. This procedure works whether W is dichotomous or continuous. Moderation is also popularly known as interaction. If X's effect on Y is moderated by W, then X and W interacted. The Johnson-Neyman technique is also called a floodlight analysis [44], which analytically derives the values of W, if they exist, that identify points of transition along the continuum of the moderator between a statistically significant and non-significant effect of X on Y. These points of the transition regions are of significance for the effect of X-the range of the moderator W where X is significantly related to Y and where it is not.

Neuroimaging biomarker for classifying AD spectrum population

Next, these altered regional FC strengths based on the *APOE* genotype were employed to classify the AD spectrum population, as previously described in publications [45, 46]. The predictive value was estimated with receiver operating characteristic (ROC) curves by calculating the sensitivity, specificity, and area under the curve (AUC). To assess the accuracy of the classification, we used the permutation test to cross-validate the ROC results because of the limited sample size in the present study. The error estimate of the permutation test was used to determine whether the observed difference between the sample means is large enough to reject the null hypothesis that the two groups have identical probability distributions. This entire process is repeated 1000 times, thereby yielding an unbiased estimation of the classification error rate. Unless specifically mentioned, the threshold for statistical significance was defined as $p < 0.05$. It was noted that we selected significant regions as classification features from the same dataset, this result will need to be validated on a novel dataset for significance. The purpose of this ROC analysis was to perform a preliminary proof of concept that a classification may be work.

RESULTS

Demographic information and neuropsychological data

As shown in Table 1, no significant differences were found in age, gender, or education among all the participants (all $p > 0.05$). The GM volumes were smaller in patients with AD compared to CN, EMCI, and LMCI subjects. A significant main effect of the disease status was shown in the MMSE and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) scores. Specifically, compared with CN subjects, LMCI subjects and AD subjects displayed a significant decrease in MMSE scores and a gradually increase in the ADAS-cog scores. Furthermore, AD subjects exhibited significantly higher ADAS-cog scores than that of LMCI subjects. The main effect of the *APOE* genotype was also shown by the *APOE* ε4 carriers representing lower scores in the MMSE scores than that of *APOE* ε4 non-carriers.

Main effects of the APOE genotype and disease status on the DMN

The main effect of the *APOE* genotype on the DMN was primarily located in the bilateral dorsolateral prefrontal cortex (DLPFC), right parahippocampal gyrus (PHG), precentral gyrus (PreCG), left hippocampus and temporal pole (TP), as described in Fig. 1A. Compared with *APOE* ε4 non-carriers, *APOE* ε4 carriers showed significantly weaker intrinsic FC in these regions, as illustrated in Fig. 1B.

The main effect of the disease was widely observed in the bilateral precuneus (PCUN) and lingual gyrus (LG), subcentral area (SCA), posterior middle temporal gyrus (pMTG), middle/inferior temporal gyrus (M/ITG), temporal-parietal junction (TPJ), PHG, and anterior medial prefrontal cortex (aMPFC), as shown

Table 1
Demographic information and neuropsychological performance

| | CN | | EMCI | | LMCI | | AD | | p-value | | |
	ε4+ (n = 14)	ε4- (n = 32)	ε4+ (n = 26)	ε4- (n = 26)	ε4+ (n = 17)	ε4- (n = 24)	ε4+ (n = 22)	ε4- (n = 8)	Gene	Disease	Disease × gene interaction
Age (y)	71.81 ± 4.13	75.22 ± 6.29	70.33 ± 6.60	72.13 ± 6.83	70.91 ± 7.37	71.91 ± 8.78	74.65 ± 6.21	68.89 ± 6.96	0.93	0.41	0.07
Education (y)	16.57 ± 2.44	15.94 ± 2.18	15.62 ± 2.91	15.58 ± 2.64	17.82 ± 2.13	15.92 ± 2.83	15.45 ± 2.89	16.00 ± 2.56	0.25	0.11	0.24
Gender (F/M)	6/8	14/18	11/15	10/16	9/8	15/9	10/12	5/3			0.71
GMVs (ml)	574.60 ± 50.76	572.60 ± 46.77	571.31 ± 55.48	577.01 ± 48.89	553.76 ± 50.48	569.05 ± 36.16	516.34 ± 69.11	560.73 ± 51.53	0.07	0.031[cef]	0.36
MMSE	28.43 ± 1.70	28.88 ± 1.16	27.77 ± 1.99	28.65 ± 1.41	27.53 ± 1.87	27.75 ± 1.48	22.36 ± 2.30	22.88 ± 3.14	0.03	<0.001[bcef]	0.97
ADAS-cog	8.83 ± 3.06	9.48 ± 4.15	13.15 ± 5.91	12.12 ± 4.89	18.82 ± 6.63	15.60 ± 6.90	34.82 ± 9.57	33.38 ± 9.10	0.09	<0.001[abcdef]	0.31

Significant differences were found in MMSE and ADAS-Cog among all groups. p values were obtained by 2×4 ANCOVA (with APOE genotype and disease status) analysis except for gender (χ² test). a–f) post-hoc analysis (Bonferroni correction) further revealed the source of ANCOVA difference. a) EMCI versus CN; b) LMCI versus CN; c) AD versus CN; d) EMCI versus LMCI; e) EMCI versus AD; f) LMCI versus AD), ε4+, APOE ε4 carriers; ε4-, APOE ε4 non-carriers; CN, cognitive normal; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; AD, Alzheimer's disease; F/M, female/male; GMVs, gray matter volumes; ml, milliliter; MMSE, Mini-Mental State Examination; ADAS-Cog, 13-item Alzheimer's Disease Assessment Scale-Cognitive subscale.

in Fig. 1C. Interestingly, according to the progressive stages of the AD spectrum, the distribution of the DMN FC presented a disturbed pattern with dynamic and robust changes, especially in the EMCI and LMCI stages. Briefly, the distributed pattern in the bilateral PCUN, left SCA and TPJ, and right PHG seemed more likely to have an inverted U-shaped, while the distribution in the bilateral LG, left MTG, and right aMPFC was more likely to have a U-shape. In addition, the FC strength in the left pMTG represented a distinctive pattern that decreased initially in the EMCI stage, then compensated in the LMCI stage but finally straightforwardly declined in the AD stage compared to that in the CN subjects, as detailed in Fig. 1D.

The neural effects of the APOE genotype × disease interaction were primarily seen in the left MTG, dorsal anterior cingulate cortex (dACC), hippocampus, right fusiform areas (FFA), inferior frontal gyrus (IFG), INS, PCUN, and DLPFC, as seen in Fig. 2A. More importantly, compared to APOE ε4 non-carriers, the APOE ε4 carriers produced approximately opposite trajectory changes in the DMN across the AD spectrum, especially in the EMCI and LMCI stages. Specifically, the APOE ε4 carriers represented increased connectivity in the left MTG, hippocampus, dACC, and right PCUN, as well as decreased connectivity in the right IFG, INS, DLPFC, and FFA from the EMCI to LMCI, while the APOE ε4 non-carriers showed a completely inverted mode, as displayed in Fig. 2B.

Behavioral significance

As shown in Fig. 3, the regression analysis displayed that the PCC-RPCUN ($R^2 = 0.082$, β = 5.872 [0.613–11.132, 95% CI], $t = 2.237$, $p = 0.029$), PCC-RINS ($R^2 = 0.117$, β = 6.523 [1.716–11.330, 95% CI], $t = 2.719$, $p = 0.009$) and PCC-RFFA ($R^2 = 0.077$, β = 5.893 [0.421–11.366, 95% CI], $t = 2.157$, $p = 0.035$) significantly affected the MMSE scores across the disease groups in the APOE ε4 non-carriers. It is interesting that the results were not significant in the APOE ε4 carriers.

Mediation and moderation analysis

The mediation yielded no significant results, as described in Supplementary Figure 2. The moderation process analysis revealed that PCC-RFFA connectivity significantly moderated the effects of the APOE genotype on the cognitive performance
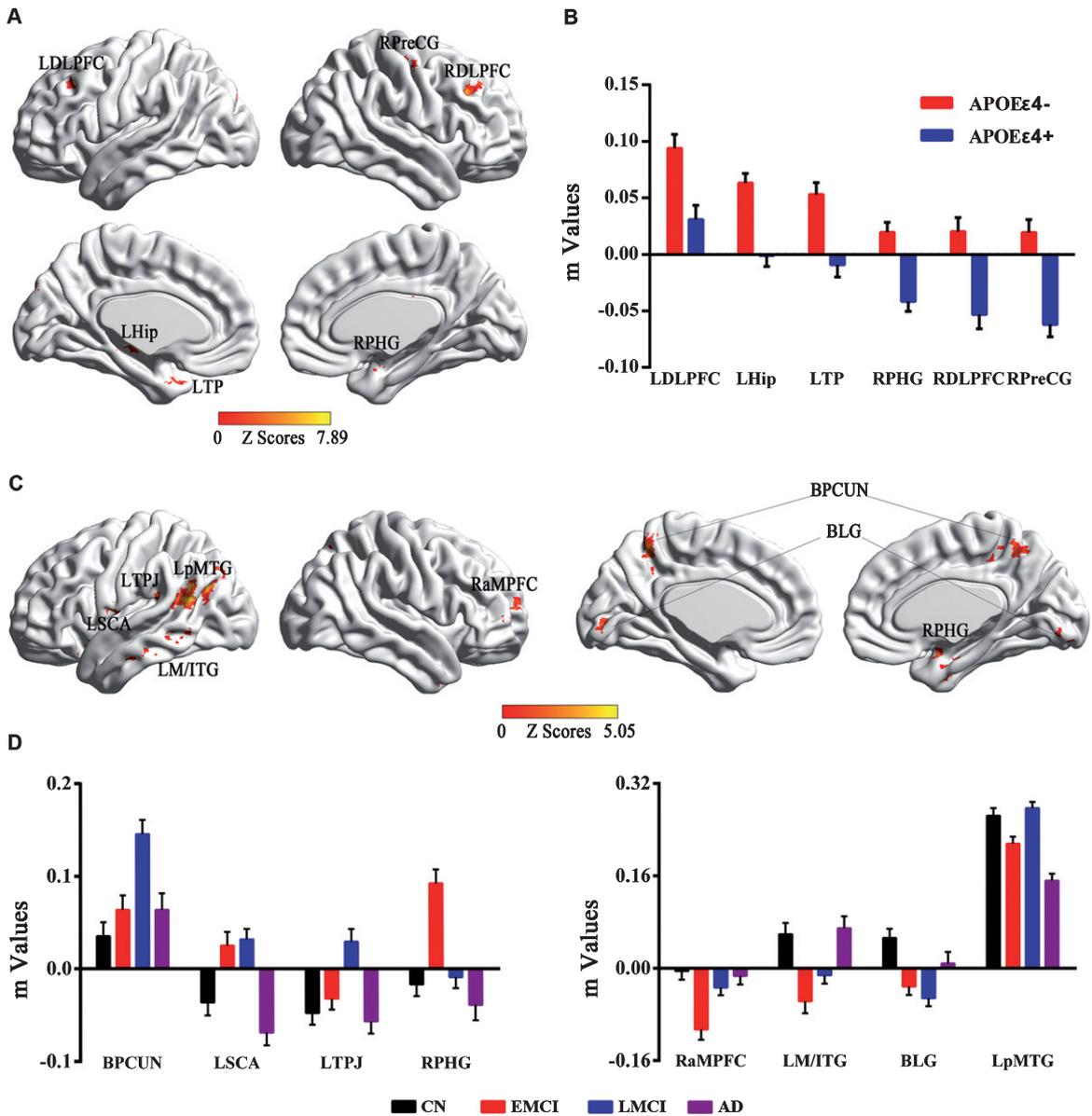
Fig. 1. Main effects of *APOE* genotype and disease status on the DMN across all subjects. A) Brain regions with main effects of *APOE* genotype revealed that altered DMN FC were primarily located in the bilateral frontal-temporal system in *APOE ε*4 carriers (*APOE ε*4+) compared to *APOE ε*4 non-carriers (*APOE ε*4–). B) Numerical representations of the significant main effect of *APOE* genotype on the DMN were described using bar charts (m is z value from the cross-correlation coefficient after Fisher's z transformed, same below). C) Brain regions with main effects of disease status revealed that altered DMN FC were primarily located in the bilateral frontal-parietal system and temporal-occipital system among four groups. D) Numerical representations of main effects of disease status on the DMN among all the groups were illustrated with bar charts. According to the progressive stages of the AD spectrum, the distribution of the DMN FC presented a disturbed pattern with U-shaped and inverted U-shaped trajectories. DMN, default mode network; FC, functional connectivity; LDLPFC, left dorsolateral prefrontal cortex; RDLPFC, right dorsolateral prefrontal cortex; LHip, left hippocampus; LTP, left temporal pole; RPreCG, right precentral gyrus; RPHG, right parahippocampal gyrus; BPCUN, bilateral precuneus; BLG, bilateral lingual gyrus; LSCA, left subcentral area; LpMTG, left posterior middle temporal gyrus; LM/ITG, left middle/inferior temporal gyrus; LTPJ, left temporal-parietal junction; RaMPFC, right anterior medial prefrontal cortex; CN, cognitive normal; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; AD, Alzheimer's disease.
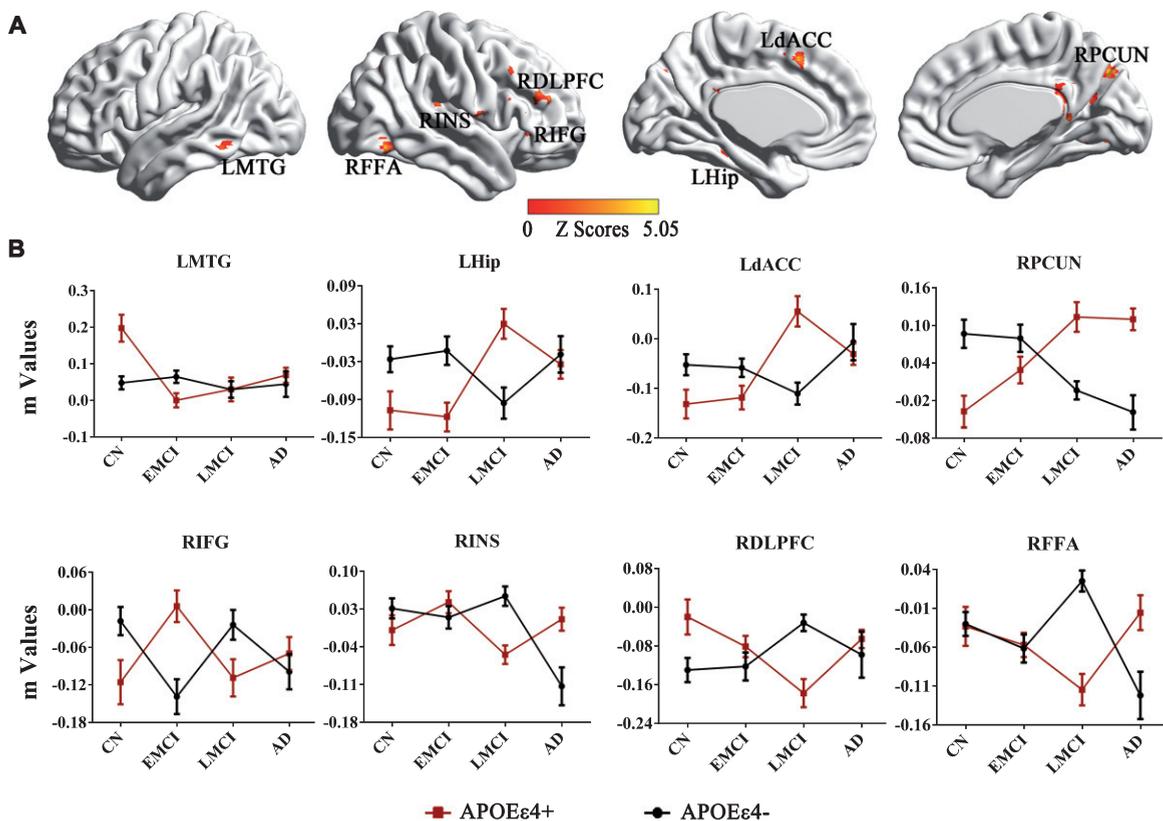
Fig. 2. Interactive effects of the *APOE* genotype and disease status on the DMN across all subjects. A) Brain regions with significant interactions between *APOE* genotype and disease status on the DMN across all subjects. B) Numerical representations of the significant interactive effects of *APOE* genotype and disease status on the DMN were illustrated with line charts. Importantly, the trend for changed DMN FC strength is opposite in *APOE ε*4 carriers (*APOE ε*4+) compared to *APOE ε*4 non-carriers (*APOE ε*4–) across the AD spectrum. DMN, default mode network; FC, functional connectivity; LMTG, left middle temporal gyrus; LHip, left hippocampus; LdACC, left dorsal anterior cingulate cortex; RPCUN, right precuneus; RIFG, right inferior frontal gyrus; RINS, right insula; RDLPFC, right dorsolateral prefrontal cortex; RFFA, right fusiform areas; CN, cognitive normal; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; AD, Alzheimer's disease.

across the disease groups. As seen in Fig. 4A, moderator variable PCC-RFFA connectivity influenced the magnitude of causal effect of *APOE* genotype on cognitive performance. As depicted in Fig. 4B, an association between two variables (*APOE* genotype and MMSE) was moderated when its size or sign depends on the third variable (PCC-RFFA connectivity). Specially, the interaction of *APOE* genotype and PCC-RFFA connectivity affected cognitive performance. Further, the Johnson-Neyman technique was applied to visualize this modulation pattern. As shown in Fig. 4C, we identified a significantly negative relationship of PCC-RFFA moderating the effects of the *APOE* genotype on the cognitive performance. That is, the *APOE* genotype produced a statistically significant and negative effect on cognitive performance with an increase in the PCC-RFFA connectivity. More importantly, we also found this

modulation effect only existed when the PCC-RFFA value was larger than –0.0823. This result indicates that the PCC-RFFA strength is above this value and the moderating effect is significant.

Stage-dependent neuroimaging biomarker for classifying AD spectrum population

We further demonstrated that DMN FC could be used to establish classification criteria with ROC curves using Fisher's linear discriminant analysis. As illustrated in Fig. 5, this classification presented a higher sensitivity and specificity dependent on the *APOE* genotype and disease stage, but not on the entire course of the AD spectrum. For example, *APOE ε*4 non-carriers presented in the AUC are 0.798 [0.680–0.916, 95% CI] and 0.811 [0.687–0.935, 95% CI] for PCC-BPCUN, 0.912 [0.804–1.019, 95% CI]
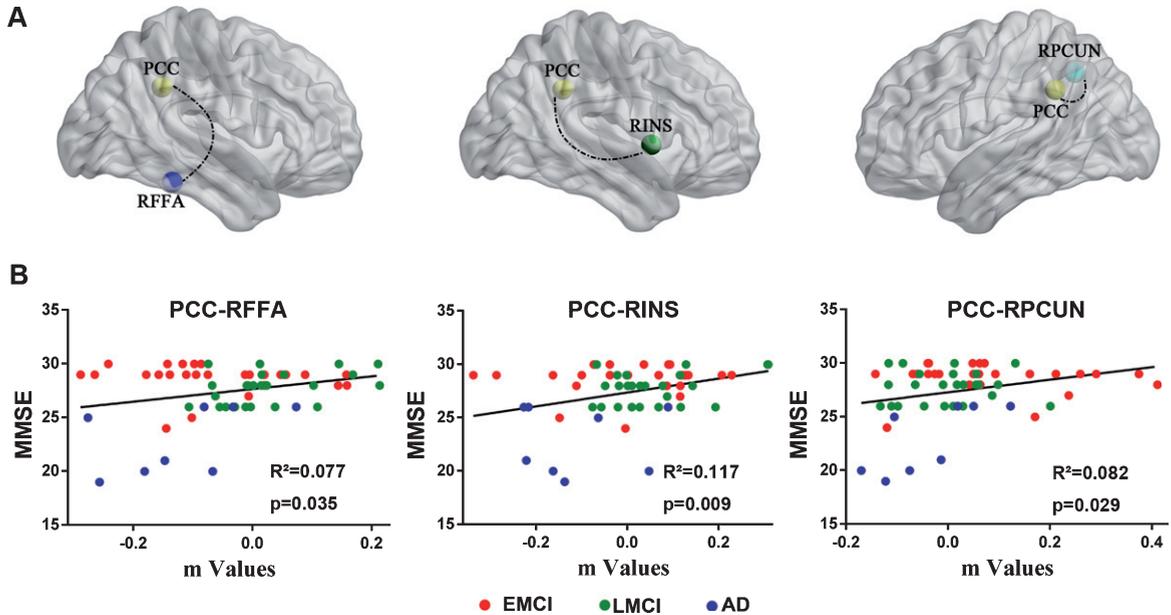
Fig. 3. Linear regression analysis identified that altered DMN FC was associated with MMSE scores in the *APOE* ε4 non-carriers but not in the *APOE* ε4 carriers. A) Brain regions with altered FC values between the PCC and RPCUN, RINS, and RFFA were significant factors affect the MMSE scores in the *APOE* ε4 non-carriers. B) Quantitatively illustration of the regression analysis results between PCC connecting with above target regions (m values) and MMSE scores across the disease groups. DMN, default mode network; FC, functional connectivity; MMSE, Mini-Mental State Examination; PCC, posterior cingulate cortex; RPCUN, right precuneus; RINS, right insula; RFFA, right fusiform areas; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; AD, Alzheimer's disease.

and 0.947 [0.870–1.024, 95% CI] for PCC-LAG, while the *APOE* ε4 carriers presented in the AUC are 0.725 [0.571–0.880, 95% CI] for PCC-LPreCG, 0.762 [0.621–0.904, 95% CI] for PCC-RINS, 0.789 [0.648–0.929, 95% CI] for PCC-RPHG, and 0.797 [0.673–0.921, 95% CI] for PCC-LAG, to discriminate the CN from EMCI, EMCI from LMCI, AD from LMCI, and AD from EMCI, respectively. All AUC values are more than 0.7, suggesting that these variables significantly discriminate the four groups. Additionally, this classifier was cross-validated by the permutation test.

DISCUSSION

AD is characterized by both structural and functional disruption connectivity [47]. In this study, we demonstrated the interaction of the *APOE* genotype and disease status and the divergent trajectory of the DMN pattern in the *APOE* ε4 carriers compared to *APOE* ε4 non-carriers in the AD continuum. This dichotomous pattern indicates that there are discrepant spatial and temporal patterns of progression within these selectively vulnerable brain regions in AD. More importantly, we identified that PCC-RFFA

connectivity conditionally moderates the effects of the *APOE* genotype on cognitive performance. Furthermore, we also determined that these altered DMN FCs could classify the AD spectrum population with good sensitivity and specificity and represent a potential neuroimaging biomarker in the disease stage-dependent manner.

Consistent with previous studies [48, 49], we identified the neural correlates of *APOE* genotype and disease status on the DMN in the AD spectrum population. These regions were frequently reported as key hubs of DMN with high FC, conveying the effective information processing in function and preferentially associated with Aβ deposition. Thus, these brain areas are vulnerable in patients with AD [20, 50–52]. Growing lines of evidence have suggested that these disrupted DMN connectivities may allow for an early prediction of progression, an assessment of prognosis, and the ability to monitor the efficacy of treatment in patients with AD [53–56]. However, it is notable that during the different stages of AD spectrum, the distributions of altered DMN FCs in the BPCUN, LSCA, LTPJ, and RPHG were more likely to be an inverted U-shape, indicating that the FC strength was initially increased in the MCI stage but decreased towards a CN trend in the AD stage. These

A

B

C
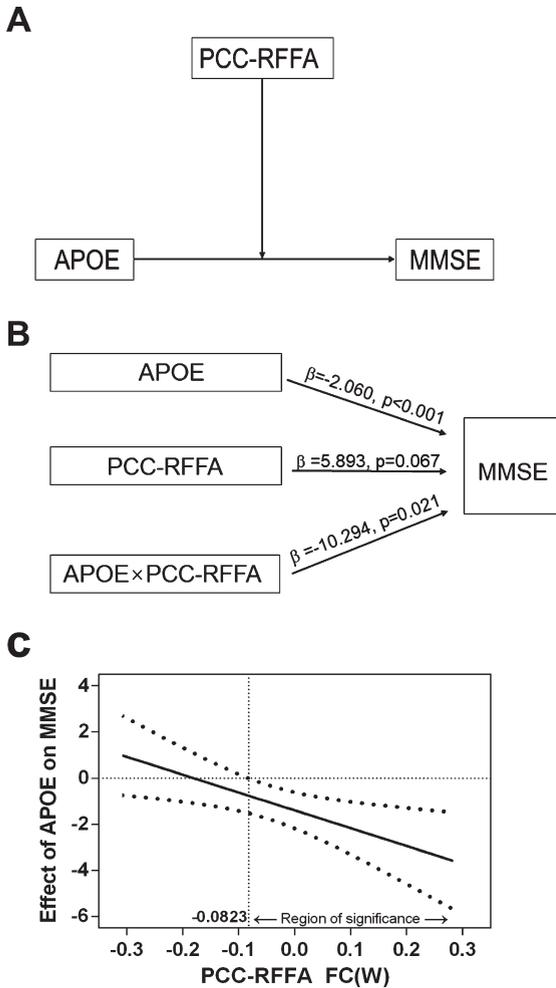
Fig. 4. Moderation process analysis. A) The moderation model with PCC-RFFA connectivity influencing the effect of *APOE* genotype on MMSE. The vertical arrow indicates the PCC-RFFA connectivity moderating the effect of *APOE* genotype on MMSE. B) A statistical diagram presents the effect of *APOE* genotype, PCC-RFFA connectivity, and interaction of *APOE* genotype with PCC-RFFA connectivity on MMSE. C) Johnson-Neyman method was applied to present the association between the *APOE* genotype and MMSE. The black continuous lines showed the conditional effects of *APOE* genotype on MMSE depending on the PCC-RFFA FC values. When the PCC-RFFA FC value is above –0.0823, the conditional effect is statistically significant ($p < 0.05$). In addition, the dotted lines above and below indicate the corresponding 95% confidence intervals (CI). The gray vertical dashed line identifies the regions of significance, reaching from the lowest score until the value of PCC-RFFA FC to change at which the lower 95% CI of the slope crosses the zero point. FC, functional connectivity; MMSE, Mini-Mental State Examination; PCC, posterior cingulate cortex; RFFA, right fusiform areas.

changing FC strengths may have a compensatory enhancement in the MCI stage and decompensation in the AD stage [57, 58]. Conversely, the distribution of altered DMN FCs represented a U-shape in

the RaMPFC, LMTG, and bilateral LG, indicating that the FC strength was initially decreased in the MCI stage but increased toward a CN trend in the AD stage. These results suggest that the functional network is disrupted, but compensation may occur in the AD phase [59–63]. However, it is interesting that the FC strength in the LpMTG presented different patterns: a decrease in the EMCI stage and an increase in the LMCI stage, but finally declining much more compared to that in the CN subjects. These dichotomous patterns in the distribution of DMN may reflect a stable property of the underlying network architecture and resulting activity fluctuations may convey preferentially vulnerability in the AD spectrum population [52]. Intriguingly, an interactive effect between diseases and the *APOE* genotype was observed in the frontal-parietal-temporal system, which is often associated with the executive control network and salience network [13, 64]. More importantly, these brain regions have been consistently identified as being involved in AD progression [52, 65]. However, the *APOE* ε4 carriers and *APOE* ε4 non-carriers produced approximately opposite FC changes with PCC to these target regions across the AD spectrum, which might be ascribed to different neural mechanisms involved in AD progression. Specifically, the *APOE* ε4 carriers in the EMCI group showed an increased FC, while the *APOE* ε4 non-carriers showed a decreased connectivity within specific regions such as LMTG, LHip, LdACC, and RPCUN. Similar changes have been reported in MCI patients [66]. The functional disruption of the DMN in patients with AD was initially targeted to the medial temporal lobe and PCC/precuneus and subsequently worsened and extended to the lateral parietal and medial frontal regions with increasing disease severity [18, 67–70]. Recently, the hypothesis of cascading network failure was proposed in the AD spectrum [20, 21]. This model suggests that the PCC, as the first target region, initiates the continuous cascade network and then shifts the processing burden to the other backbone regions throughout the AD spectrum. These backbone regions with high connectivity to the posterior DMN are associated with amyloid protein accumulation [71–73]. In addition, the cascading failures network is characterized by local overloading, eventually leading to the entire DMN and systems failing, which precedes structural and functional declines in the AD spectrum [21]. These findings strongly indicate that the stage between EMCI and LMCI was more sensitive and vulnerable in the preclinical patients with AD. The important connectivities

within DMN were disrupted likely fromAβ plaque-associated neuronal toxicity. And then, this toxicity usually triggers a cascade of cellular changes, including hyperphosphorylation of tau, oxidative damage, synaptic failure, and inflammation [74–76]. More importantly, we also demonstrated a positive correlation between the altered DMN FC and changes in the MMSE scores across the disease groups. That is, the more increased connectivity in the PCC-RPCUN, PCC-RINS, and PCC-RFFA, the less the MMSE decreased. Although the general trend of the MMSE scores was decreased from EMCI, LMCI to AD, the increased connectivity within PCC-RPCUN, PCC-RINS, and PCC-RFFA was diminished and did not reverse the decrement of MMSE at the individual level, which might also support the compensation theory of AD [77, 78]. It is noted that this correlation was only observed in *APOE* ε4 non-carriers, indicating that the relationship between the general mental status and brain function is tightly coupled in *APOE* ε4 non-carriers but with a loss of functional coupling in the *APOE* ε4 carriers. Ye et al. [79] also found that the increased hippocampal FC was positively correlated with changes in episodic memory test scores in aMCI patients with *APOE* ε4 non-carriers but not in the *APOE* ε4 carriers. These findings highlight that the *APOE* genotype may modulate the intrinsic effects of brain function at the different levels and divergences in the risk of progressing to AD.

Next, a conditional modulation analysis identified that the DMN FC could moderate the relationship between the *APOE* genotype and cognitive performance. This result provides a new perspective on the mechanisms that facilitate interactions between the complex genetic risk factors and cognitive impairment. Accumulated evidence has reported the relationship between the *APOE* genotype and cognitive function in patients with MCI or AD [79–87]. Several studies have revealed that the genotype-behavior relationship was modulated by brain structure and function with mediation analysis. For example, Kerchner et al. [25] found that hippocampal CA1 atrophy might be associated with the *APOE* ε4 allele phenotypic effects on memory function in AD or aMCI patients. Our group found that amygdala FC strength regulated the effects of the *APOE* genotype and age on cognitive function in aMCI patients [88]. Combined with multiple genetic loci in the dopamine pathway, nucleus accumbens FC mediates the association between multiple genetic loci effects and anxious depression in major depressive disorder patients [89].

Currently, the data revealed that *APOE* genotype has substantial effect on the MMSE scores and the effect is moderated by intrinsic PCC-RFFA. This suggested that intrinsic DMN activity modulate the effects of *APOE* genotypes on the behavioral performance. Through a combined resting-state functional and structural MRI study, He et al. [90] found altered low-frequency blood oxygenation level-dependent fluctuations coherence in the FFA in patients with AD. Additionally, both AD and MCI patients represented changes in the FFA functional activation during a visual working memory task compared to normal controls [91]. FFA, as a cortical center, shows co-activation when performing the facial matching task [92, 93] in normal agingand MCI patients. Moreover, considering the pathologic mechanism, Guillozet et al. [94] demonstrated that there were neurofibrillary tangles in the FFA regionin normal agingand MCI patients, and MCI patients produced more neurofibrillary tangles than those in normal control subjects. These studies showed that an FFA lesion in structure and function may preferentially contribute to AD development, especially in visual cognition. Taken together, these findings strongly indicate that intrinsic PCC-RFFA may bridge the relationship between the *APOE* genotype and complex brain function and construct the gene-brain-behavior mode across the disease groups.

There are some studies that have tried to establish biomarkers to distinguish different stages of the AD spectrum. Penn Biomarker Core have developed a pathological CSF and plasma biomarker signature for mild AD as well as a biomarker that predicts progression from MCI and/or CN to AD [95]. MRI patterns of brain atrophy (quantified by the SPARE-AD index) and ADAS-cog were reported to have a similar predictive value in the progression from MCI to AD, and their combination was better than their individual performance [96]. The combination of SPARE-AD, ADAS-cog, and the *APOE* genotype provided the highest hazard ratio in predicting the progression from MCI to AD [97]. With a large-scale network analysis based on the rs-fMRI, interconnectivity patterns of the entire brain regions can be used to classify subjects with AD, aMCI, and CN [98]. Here, we verified that altered DMN FC as candidate biomarkers could possibly classify AD and EMCI subjects (AUC = 94.7%) or AD and LMCI subjects (AUC = 91.2%) by detecting PCC-LpMTG connectivity, and classify CN and EMCI (AUC = 79.8%) or EMCI and LMCI (AUC = 81.1%) by measuring the PCC-BPCUN connectivity in *APOE* ε4 non-carriers,
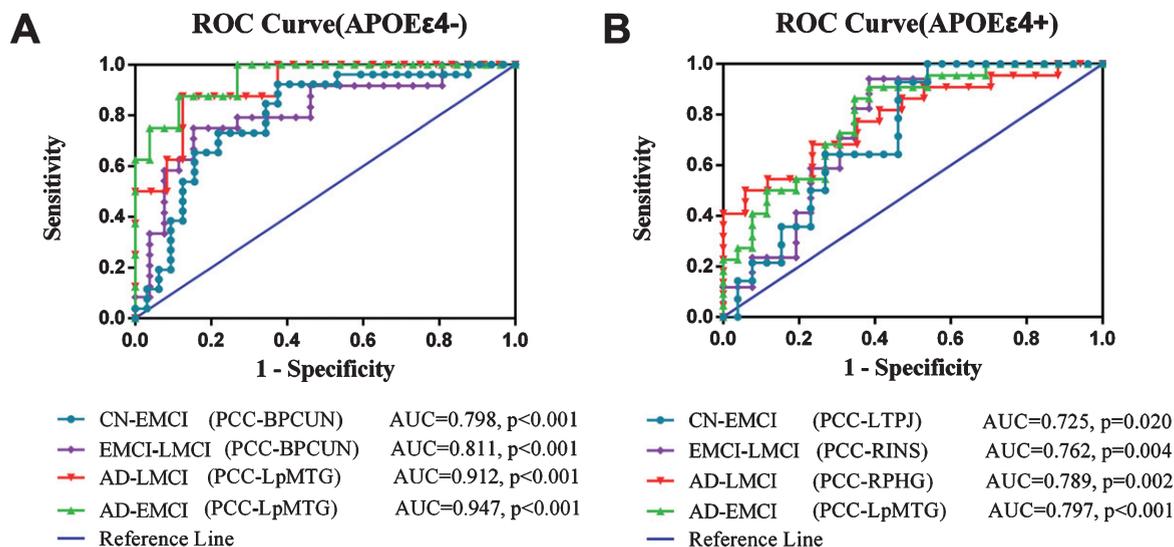
Fig. 5. Stage-dependent neuroimaging biomarker for classifying AD spectrum population. A) In *APOE ε*4 non-carriers, the value of FC is a measure of the predictability of the variable in classifying EMCI and CN (AUC value = 0.798, p < 0.001 for PCC-BPCUN), EMCI and LMCI (AUC value = 0.811, p < 0.001 for PCC-BPCUN), AD and LMCI (AUC value = 0.912, $p < 0.001$ for PCC-LpMTG), AD and EMCI (AUC value = 0.947, $p < 0.001$ for PCC-LpMTG). B) In *APOE ε*4 carriers, the value of FC is a measure of the predictability of the variable in classifying EMCI and CN (AUC value = 0.725, $p = 0.020$ for PCC-LTPJ), EMCI and LMCI (AUC value = 0.762, $p = 0.004$ for PCC-RINS), AD and LMCI (AUC value = 0.789, $p = 0.002$ for PCC-RPHG), AD and EMCI (AUC value = 0.797, $p < 0.001$ for PCC-LpMTG). ROC, receiver operating characteristic; FC, functional connectivity; PCC, posterior cingulate cortex; BPCUN, bilateral precuneus; LpMTG, left posterior middle temporal gyrus; LTPJ, left temporal-parietal junction; RINS, right insula; RPHG, right parahippocampal gyrus; LpMTG, left posterior middle temporal gyrus; AUC, area under curve; CN, cognitive normal; EMCI, early mild cognitive impairment; LMCI, late mild cognitive impairment; AD, Alzheimer's disease.

while in the *APOE ε*4 carriers the AUC values were more than 0.7. This suggests that the intrinsic connectivity yields a high level of accuracy in discriminating the AD spectrum population, which preferentially depends on the different pathological stage. Notably, no DMN FC could distinguish the four group populations at one time. Thus, the changes in the DMN FC strengths can serve as a neuroimaging biomarker at the preclinical stage to monitor the progression of the disease in a stage-dependent manner. In addition, the sensitivity of the ROC curve in the *APOE ε*4 non-carriers is higher than that of *APOE ε*4 carriers. We postulate that the brain network trajectory in the *APOE ε*4 carriers is obviously disrupted and destructive, and such a trajectory thereby results in less sensitivity at differentiating the pathological stage of AD [33, 99–101]. To date there are no clinically applicable non-invasive biomarker for detecting the early stages of AD spectrum [102, 103]. Positron emission tomography (PET) imaging of amyloid exposes patients to radiation and injection of radioactive agents and the cost is expensive [104, 105]. The limitation of measuring Aβ or tau from CSF or plasma is invasive process of sample collecting. And there is no guarantee of complete specificity and sensitivity for

an early diagnosis or differential diagnosis from other dementias [103]. The transitions between stages of AD spectrum are subtle, and individuals may report cognitive decline even if neuropsychological tests do not show any impairment [106]. Given these facts, the diagnostic biomarkers should be easy to measure, preferably non-invasive, and widely available. The shift can be from invasive biomarkers of CSF and PET to blood biomarkers and MRI techniques [107–109]. Our results suggested that apart from generalcognitivefunctioning to be tested,for some patients that are difficult to assess or stagediagnosis, detecting the *APOE* genotype from patients' blood samples and neuroimaging biomarkers derived from DMN connectivity data in rs-fMRI could provide objective evidence. The framework for integrating multi-level (*APOE* genotypes and DMN connectivity) biomarkers may help diagnose the stages of AD spectrum.

The present study has some limitations. First, this study is a cross-sectional design, and follow-up studies should be conducted to determine whether the altered FC identified here could be used as a stable biomarker for predicting AD progression. Second, only 8 *APOE ε*4 non-carriers in patients with AD were recruited, and this fact may limit the general

use of the current findings, so more subjects should be enrolled in future studies. Third, previous genetic studies have identified some vulnerable genes that were related to cognitive impairment and affected by the resting-state brain function [110, 111]. Future research should explore the polygenetic effects on brain function by using a multilocus genetic imaging approach. Fourth, we use the significant DMN connectivity from our regression analysis to conduct a classification analysis. And we have found that these data could predict the progression of AD. It should be interpreted with caution because these data come from the same dataset. This is an exploratory classification method and we need to demonstrate this technique on a new dataset in the future study. Finally, it should be noted that this study is limited on the posterior DMN, and future work is necessary to investigate how the *APOE* genotype regulates anterior DMN or extend to other intrinsic connectivity networks.

Conclusions

We demonstrated different trajectories of DMN FC between *APOE ε*4 carriers and *APOE ε*4 non-carriers on the AD spectrum population. A moderation analysis revealed that intrinsic DMN connectivity could regulate the effects of the *APOE* genotype on cognitive impairment. Additionally, we propose that the DMN FC strength might be useful as imaging biomarkers for classifying the stages of the AD spectrum. These findings directly reveal the intrinsic effects of the *APOE* genotype on brain function and might provide novel insights into the mechanisms driving AD progression.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/19-0254r1).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/JAD-190254.

REFERENCES

[1] Jack CR, Jr., Knopman DS, Weigand SD, Wiste HJ, Vemuri P, Lowe V, Kantarci K, Gunter JL, Senjem ML, Ivnik RJ, Roberts RO, Rocca WA, Boeve BF, Petersen RC (2012) An operational approach to National Institute on Aging-Alzheimer's Association criteria for preclinical Alzheimer disease. *Ann Neurol* **71**, 765-775.

[2] Jack CR, Jr., Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, Holtzman DM, Jagust W, Jessen F, Karlawish J, Liu E, Molinuevo JL, Montine T, Phelps C,

Rankin KP, Rowe CC, Scheltens P, Siemers E, Snyder HM, Sperling R (2018) NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement* **14**, 535-562.

[3] Cummings J (2019) The National Institute on Aging-Alzheimer's Association Framework on Alzheimer's disease: Application to clinical trials. *Alzheimers Dement* **15**, 172-178.

[4] Sperling RA, Jack CR, Jr., Aisen PS (2011) Testing the right target and right drug at the right stage. *Sci Transl Med* **3**, 111cm133.

[5] Atri A (2019) The Alzheimer's disease clinical spectrum: Diagnosis and management. *Med Clin North Am* **103**, 263-293.

[6] Smith AD, Yaffe K (2014) Dementia (including Alzheimer's disease) can be prevented: Statement supported by international experts. *J Alzheimers Dis* **38**, 699-703.

[7] Sperling R, Mormino E, Johnson K (2014) The evolution of preclinical Alzheimer's disease: Implications for prevention trials. *Neuron* **84**, 608-622.

[8] Mitchell AJ (2009) CSF phosphorylated tau in the diagnosis and prognosis of mild cognitive impairment and Alzheimer's disease: A meta-analysis of 51 studies. *J Neurol Neurosurg Psychiatry* **80**, 966-975.

[9] Koivunen J, Scheinin N, Virta JR, Aalto S, Vahlberg T, Nagren K, Helin S, Parkkola R, Viitanen M, Rinne JO (2011) Amyloid PET imaging in patients with mild cognitive impairment: A 2-year follow-up study. *Neurology* **76**, 1085-1090.

[10] Aisen PS, Petersen RC, Donohue M, Weiner MW (2015) Alzheimer's Disease Neuroimaging Initiative 2 Clinical Core: Progress and plans. *Alzheimers Dement* **11**, 734-739.

[11] Aisen PS, Petersen RC, Donohue MC, Gamst A, Raman R, Thomas RG, Walter S, Trojanowski JQ, Shaw LM, Beckett LA, Jack CR, Jr., Jagust W, Toga AW, Saykin AJ, Morris JC, Green RC, Weiner MW (2010) Clinical Core of the Alzheimer's Disease Neuroimaging Initiative: Progress and plans. *Alzheimers Dement* **6**, 239-246.

[12] Weiner MW, Aisen PS, Jack CR, Jr., Jagust WJ, Trojanowski JQ, Shaw L, Saykin AJ, Morris JC, Cairns N, Beckett LA, Toga A, Green R, Walter S, Soares H, Snyder P, Siemers E, Potter W, Cole PE, Schmidt M (2010) The Alzheimer's Disease Neuroimaging Initiative: Progress report and future plans. *Alzheimers Dement* **6**, 202-211 e207.

[13] Buckner RL, Andrews-Hanna JR, Schacter DL (2008) The brain's default network: Anatomy, function, and relevance to disease. *Ann N Y Acad Sci* **1124**, 1-38.

[14] Fox MD, Raichle ME (2007) Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci* **8**, 700-711.

[15] Greicius MD, Krasnow B, Reiss AL, Menon V (2003) Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. *Proc Natl Acad Sci U S A* **100**, 253-258.

[16] Palmqvist S, Scholl M, Strandberg O, Mattsson N, Stomrud E, Zetterberg H, Blennow K, Landau S, Jagust W, Hansson O (2017) Earliest accumulation of beta-amyloid occurs within the default-mode network and concurrently affects brain connectivity. *Nat Commun* **8**, 1214.

[17] Jones DT, Machulda MM, Vemuri P, McDade EM, Zeng G, Senjem ML, Gunter JL, Przybelski SA, Avula RT, Knopman DS, Boeve BF, Petersen RC, Jack CR, Jr. (2011) Age-related changes in the default mode network

are more advanced in Alzheimer disease. *Neurology* **77**, 1524-1531.

[18] Damoiseaux JS, Prater KE, Miller BL, Greicius MD (2012) Functional connectivity tracks clinical deterioration in Alzheimer's disease. *Neurobiol Aging* **33**, 828 e819-830.

[19] Jack CR, Jr., Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, Shaw LM, Vemuri P, Wiste HJ, Weigand SD, Lesnick TG, Pankratz VS, Donohue MC, Trojanowski JQ (2013) Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. *Lancet Neurol* **12**, 207-216.

[20] Jones DT, Graff-Radford J, Lowe VJ, Wiste HJ, Gunter JL, Senjem ML, Botha H, Kantarci K, Boeve BF, Knopman DS, Petersen RC, Jack CR, Jr. (2017) Tau, amyloid, and cascading network failure across the Alzheimer's disease spectrum. *Cortex* **97**, 143-159.

[21] Jones DT, Knopman DS, Gunter JL, Graff-Radford J, Vemuri P, Boeve BF, Petersen RC, Weiner MW, Jack CR, Jr. (2016) Cascading network failure across the Alzheimer's disease spectrum. *Brain* **139**, 547-562.

[22] Lambert JC, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, DeStafano AL, Bis JC, Beecham GW, Grenier-Boley B, Russo G, Thorton-Wells TA, Jones N, Smith AV, Chouraki V, Thomas C, Ikram MA, Zelenika D, Vardarajan BN, Kamatani Y, Lin CF, Gerrish A, Schmidt H, Kunkle B, Dunstan ML, Ruiz A, Bihoreau MT, Choi SH, Reitz C, Pasquier F, Cruchaga C, Craig D, Amin N, Berr C, Lopez OL, De Jager PL, Deramecourt V, Johnston JA, Evans D, Lovestone S, Letenneur L, Moron FJ, Rubinsztein DC, Eiriksdottir G, Sleegers K, Goate AM, Fievet N, Huentelman MW, Gill M, Brown K, Kamboh MI, Keller L, Barberger-Gateau P, McGuiness B, Larson EB, Green R, Myers AJ, Dufouil C, Todd S, Wallon D, Love S, Rogaeva E, Gallacher J, St George-Hyslop P, Clarimon J, Lleo A, Bayer A, Tsuang DW, Yu L, Tsolaki M, Bossu P, Spalletta G, Proitsi P, Collinge J, Sorbi S, Sanchez-Garcia F, Fox NC, Hardy J, Deniz Naranjo MC, Bosco P, Clarke R, Brayne C, Galimberti D, Mancuso M, Matthews F, Moebus S, Mecocci P, Del Zompo M, Maier W, Hampel H, Pilotto A, Bullido M, Panza F, Caffarra P, Nacmias B, Gilbert JR, Mayhaus M, Lannefelt L, Hakonarson H, Pichler S, Carrasquillo MM, Ingelsson M, Beekly D, Alvarez V, Zou F, Valladares O, Younkin SG, Coto E, Hamilton-Nelson KL, Gu W, Razquin C, Pastor P, Mateo I, Owen MJ, Faber KM, Jonsson PV, Combarros O, O'Donovan MC, Cantwell LB, Soininen H, Blacker D, Mead S, Mosley TH, Jr., Bennett DA, Harris TB, Fratiglioni L, Holmes C, de Bruijn RF, Passmore P, Montine TJ, Bettens K, Rotter JI, Brice A, Morgan K, Foroud TM, Kukull WA, Hannequin D, Powell JF, Nalls MA, Ritchie K, Lunetta KL, Kauwe JS, Boerwinkle E, Riemenschneider M, Boada M, Hiltuenen M, Martin ER, Schmidt R, Rujescu D, Wang LS, Dartigues JF, Mayeux R, Tzourio C, Hofman A, Nothen MM, Graff C, Psaty BM, Jones L, Haines JL, Holmans PA, Lathrop M, Pericak-Vance MA, Launer LJ, Farrer LA, van Duijn CM, Van Broeckhoven C, Moskvina V, Seshadri S, Williams J, Schellenberg GD, Amouyel P (2013) Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat Genet* **45**, 1452-1458.

[23] Reiman EM, Chen K, Liu X, Bandy D, Yu M, Lee W, Ayutyanont N, Keppler J, Reeder SA, Langbaum JB, Alexander GE, Klunk WE, Mathis CA, Price JC, Aizenstein HJ, DeKosky ST, Caselli RJ (2009) Fibrillar amyloid-beta burden in cognitively normal people at

3 levels of genetic risk for Alzheimer's disease. *Proc Natl Acad Sci USA* **106**, 6820-6825.

[24] Yu L, Petyuk VA, Tasaki S, Boyle PA, Gaiteri C, Schneider JA, De Jager PL, Bennett DA (2019) Association of cortical beta-amyloid protein in the absence of insoluble deposits with Alzheimer disease. *JAMA Neurol*, doi:10.1001/jamaneurol.2019.0834.

[25] Kerchner GA, Berdnik D, Shen JC, Bernstein JD, Fenesy MC, Deutsch GK, Wyss-Coray T, Rutt BK (2014) APOE epsilon4 worsens hippocampal CA1 apical neuropil atrophy and episodic memory. *Neurology* **82**, 691-697.

[26] Tisato V, Zuliani G, Vigliano M, Longo G, Franchini E, Secchiero P, Zauli G, Paraboschi EM, Vikram Singh A, Serino ML, Ortolani B, Zurlo A, Bosi C, Greco A, Seripa D, Asselta R, Gemmati D (2018) Gene-gene interactions among coding genes of iron-homeostasis proteins and APOE-alleles in cognitive impairment diseases. *PLoS One* **13**, e0193867.

[27] Ward KM, Kraal AZ, Flowers SA, Ellingrod VL (2017) Cardiovascular pharmacogenomics and cognitive function in patients with schizophrenia. *Pharmacotherapy* **37**, 1122-1130.

[28] Agosta F, Vossel KA, Miller BL, Migliaccio R, Bonasera SJ, Filippi M, Boxer AL, Karydas A, Possin KL, Gorno-Tempini ML (2009) Apolipoprotein E epsilon4 is associated with disease-specific effects on brain atrophy in Alzheimer's disease and frontotemporal dementia. *Proc Natl Acad Sci U S A* **106**, 2018-2022.

[29] Luo X, Li K, Jia YL, Zeng Q, Jiaerken Y, Qiu T, Huang P, Xu X, Shen Z, Guan X, Zhou J, Wang C, Xu JJ, Zhang M (2019) Altered effective connectivity anchored in the posterior cingulate cortex and the medial prefrontal cortex in cognitively intact elderly APOE epsilon4 carriers: A preliminary study. *Brain Imaging Behav* **13**, 270-282.

[30] Goveas JS, Xie C, Chen G, Li W, Ward BD, Franczak MB, Jones JL, Antuono PG, Li SJ (2013) Functional network endophenotypes unravel the effects of apolipoprotein E epsilon 4 in middle-aged adults. *PLoS One* **8**, e55902.

[31] Shu H, Shi Y, Chen G, Wang Z, Liu D, Yue C, Ward BD, Li W, Xu Z, Chen G, Guo Q, Xu J, Li SJ, Zhang Z (2016) Opposite neural trajectories of apolipoprotein E 4 and 2 alleles with aging associated with different risks of Alzheimer's disease. *Cereb Cortex* **26**, 1421-1429.

[32] Yuan B, Xie C, Shu H, Liao W, Wang Z, Liu D, Zhang Z (2016) Differential effects of APOE genotypes on the anterior and posterior subnetworks of default mode network in amnestic mild cognitive impairment. *J Alzheimers Dis* **54**, 1409-1423.

[33] McKenna F, Koo BB, Killiany R (2016) Comparison of ApoE-related brain connectivity differences in early MCI and normal aging populations: An fMRI study. *Brain Imaging Behav* **10**, 970-983.

[34] Saykin AJ, Shen L, Foroud TM, Potkin SG, Swaminathan S, Kim S, Risacher SL, Nho K, Huentelman MJ, Craig DW, Thompson PM, Stein JL, Moore JH, Farrer LA, Green RC, Bertram L, Jack CR, Jr., Weiner MW (2010) Alzheimer's Disease Neuroimaging Initiative biomarkers as quantitative phenotypes: Genetics core aims, progress, and plans. *Alzheimers Dement* **6**, 265-273.

[35] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**, 939-944.

[36] Van Dijk KR, Hedden T, Venkataraman A, Evans KC, Lazar SW, Buckner RL (2010) Intrinsic functional connectivity as a tool for human connectomics: Theory, properties, and optimization. *J Neurophysiol* **103**, 297-321.

[37] Andrews-Hanna JR, Snyder AZ, Vincent JL, Lustig C, Head D, Raichle ME, Buckner RL (2007) Disruption of large-scale brain systems in advanced aging. *Neuron* **56**, 924-935.

[38] Xie C, Li SJ, Shao Y, Fu L, Goveas J, Ye E, Li W, Cohen AD, Chen G, Zhang Z, Yang Z (2011) Identification of hyperactive intrinsic amygdala network connectivity associated with impulsivity in abstinent heroin addicts. *Behav Brain Res* **216**, 639-646.

[39] Xie C, Bai F, Yuan B, Yu H, Shi Y, Yuan Y, Wu D, Zhang ZS, Zhang ZJ (2015) Joint effects of gray matter atrophy and altered functional connectivity on cognitive deficits in amnestic mild cognitive impairment patients. *Psychol Med* **45**, 1799-1810.

[40] Xie C, Goveas J, Wu Z, Li W, Chen G, Franczak M, Antuono PG, Jones JL, Zhang Z, Li SJ (2012) Neural basis of the association between depressive symptoms and memory deficits in nondemented subjects: Resting-state fMRI study. *Hum Brain Mapp* **33**, 1352-1363.

[41] Xie C, Li W, Chen G, Ward BD, Franczak MB, Jones JL, Antuono PG, Li S-J, Goveas JS (2013) Late-life depression, mild cognitive impairment and hippocampal functional network architecture. *Neuroimage Clin* **3**, 311-320.

[42] Hayes AF (2013) Introduction to mediation, moderation, and conditional process analysis: A regression-based approach. *J Educ Meas* **51**, 335-337.

[43] Hayes AF, Rockwood NJ (2017) Regression-based statistical mediation and moderation analysis in clinical research: Observations, recommendations, and implementation. *Behav Res Ther* **98**, 39-57.

[44] Spiller SA, Fitzsimons GJ, Lynch JG, Mcclelland GH (2013) Spotlights, floodlights, and the magic number zero: Simple effects tests in moderated regression. *J Mark Res* **50**, 277-288.

[45] Ranasinghe KG, Hinkley LB, Beagle AJ, Mizuiri D, Dowling AF, Honma SM, Finucane MM, Scherling C, Miller BL, Nagarajan SS, Vossel KA (2014) Regional functional connectivity predicts distinct cognitive impairments in Alzheimer's disease spectrum. *Neuroimage Clin* **5**, 385-395.

[46] Weiler M, Teixeira CV, Nogueira MH, de Campos BM, Damasceno BP, Cendes F, Balthazar ML (2014) Differences and the relationship in default mode network intrinsic activity and functional connectivity in mild Alzheimer's disease and amnestic mild cognitive impairment. *Brain Connect* **4**, 567-574.

[47] Toga AW, Thompson PM (2013) Connectomics sheds new light on Alzheimer's disease. *Biol Psychiatry* **73**, 390-392.

[48] Wu X, Li R, Fleisher AS, Reiman EM, Guan X, Zhang Y, Chen K, Yao L (2011) Altered default mode network connectivity in Alzheimer's disease–a resting functional MRI and Bayesian network study. *Hum Brain Mapp* **32**, 1868-1881.

[49] Lee ES, Yoo K, Lee YB, Chung J, Lim JE, Yoon B, Jeong Y (2016) Default mode network functional connectivity in early and late mild cognitive impairment: Results from the

Alzheimer's Disease Neuroimaging Initiative. *Alzheimer Dis Assoc Disord* **30**, 289-296.

[50] Wang Y, Risacher SL, West JD, McDonald BC, Magee TR, Farlow MR, Gao S, O'Neill DP, Saykin AJ (2013) Altered default mode network connectivity in older adults with cognitive complaints and amnestic mild cognitive impairment. *J Alzheimers Dis* **35**, 751-760.

[51] Hedden T, Van Dijk KR, Becker JA, Mehta A, Sperling RA, Johnson KA, Buckner RL (2009) Disruption of functional connectivity in clinically normal older adults harboring amyloid burden. *J Neurosci* **29**, 12686-12694.

[52] Buckner RL, Sepulcre J, Talukdar T, Krienen FM, Liu H, Hedden T, Andrews-Hanna JR, Sperling RA, Johnson KA (2009) Cortical hubs revealed by intrinsic functional connectivity: Mapping, assessment of stability, and relation to Alzheimer's disease. *J Neurosci* **29**, 1860-1873.

[53] Li Y, Yao H, Lin P, Zheng L, Li C, Zhou B, Wang P, Zhang Z, Wang L, An N, Wang J, Zhang X (2017) Frequency-dependent altered functional connections of default mode network in Alzheimer's disease. *Front Aging Neurosci* **9**, 259.

[54] Sole-Padulles C, Bartres-Faz D, Llado A, Bosch B, Pena-Gomez C, Castellvi M, Rami L, Bargallo N, Sanchez-Valle R, Molinuevo JL (2013) Donepezil treatment stabilizes functional connectivity during resting state and brain activity during memory encoding in Alzheimer's disease. *J Clin Psychopharmacol* **33**, 199-205.

[55] Lorenzi M, Beltramello A, Mercuri NB, Canu E, Zoccatelli G, Pizzini FB, Alessandrini F, Cotelli M, Rosini S, Costardi D, Caltagirone C, Frisoni GB (2011) Effect of memantine on resting state default mode network activity in Alzheimer's disease. *Drugs Aging* **28**, 205-217.

[56] Koch W, Teipel S, Mueller S, Benninghoff J, Wagner M, Bokde AL, Hampel H, Coates U, Reiser M, Meindl T (2012) Diagnostic power of default mode network resting state fMRI in the detection of Alzheimer's disease. *Neurobiol Aging* **33**, 466-478.

[57] Ye Q, Chen H, Su F, Shu H, Gong L, Xie C, Zhou H, Bai F (2018) An inverse U-shaped curve of resting-state networks in individuals at high risk of Alzheimer's disease. *J Clin Psychiatry* **79**, 17m11583.

[58] Rao SM, Bonner-Jackson A, Nielson KA, Seidenberg M, Smith JC, Woodard JL, Durgerian S (2015) Genetic risk for Alzheimer's disease alters the five-year trajectory of semantic memory activation in cognitively intact elders. *Neuroimage* **111**, 136-146.

[59] Qi Z, Wu X, Wang Z, Zhang N, Dong H, Yao L, Li K (2010) Impairment and compensation coexist in amnestic MCI default mode network. *Neuroimage* **50**, 48-55.

[60] Stern Y, Moeller JR, Anderson KE, Luber B, Zubin NR, DiMauro AA, Park A, Campbell CE, Marder K, Bell K, Van Heertum R, Sackeim HA (2000) Different brain networks mediate task performance in normal aging and AD: Defining compensation. *Neurology* **55**, 1291-1297.

[61] Frantzidis CA, Vivas AB, Tsolaki A, Klados MA, Tsolaki M, Bamidis PD (2014) Functional disorganization of small-world brain networks in mild Alzheimer's disease and amnestic mild cognitive impairment: An EEG study using relative wavelet entropy (RWE). *Front Aging Neurosci* **6**, 224.

[62] Gregory S, Long JD, Tabrizi SJ, Rees G (2017) Measuring compensation in neurodegeneration using MRI. *Curr Opin Neurol* **30**, 380-387.

[63] Krajcovicova L, Barton M, Elfmarkova-Nemcova N, Mikl M, Marecek R, Rektorova I (2017) Changes in connectiv-

ity of the posterior default network node during visual processing in mild cognitive impairment: Staged decline between normal aging and Alzheimer's disease. *J Neural Transm (Vienna)* **124**, 1607-1619.

[64] Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, Filippini N, Watkins KE, Toro R, Laird AR, Beckmann CF (2009) Correspondence of the brain's functional architecture during activation and rest. *Proc Natl Acad Sci U S A* **106**, 13040-13045.

[65] Smith AD (2002) Imaging the progression of Alzheimer pathology through the brain. *Proc Natl Acad Sci U S A* **99**, 4135-4137.

[66] Bai F, Zhang Z, Watson DR, Yu H, Shi Y, Yuan Y, Zang Y, Zhu C, Qian Y (2009) Abnormal functional connectivity of hippocampus during episodic memory retrieval processing network in amnestic mild cognitive impairment. *Biol Psychiatry* **65**, 951-958.

[67] Zhang HY, Wang SJ, Liu B, Ma ZL, Yang M, Zhang ZJ, Teng GJ (2010) Resting brain connectivity: Changes during the progress of Alzheimer disease. *Radiology* **256**, 598-606.

[68] Elman JA, Oh H, Madison CM, Baker SL, Vogel JW, Marks SM, Crowley S, O'Neil JP, Jagust WJ (2014) Neural compensation in older people with brain amyloid-beta deposition. *Nat Neurosci* **17**, 1316-1318.

[69] Perez-Nievas BG, Stein TD, Tai HC, Dols-Icardo O, Scotton TC, Barroeta-Espar I, Fernandez-Carballo L, de Munain EL, Perez J, Marquie M, Serrano-Pozo A, Frosch MP, Lowe V, Parisi JE, Petersen RC, Ikonomovic MD, Lopez OL, Klunk W, Hyman BT, Gomez-Isla T (2013) Dissecting phenotypic traits linked to human resilience to Alzheimer's pathology. *Brain* **136**, 2510-2526.

[70] Jagust WJ, Mormino EC (2011) Lifespan brain activity, beta-amyloid, and Alzheimer's disease. *Trends Cogn Sci* **15**, 520-526.

[71] Pasquini L, Benson G, Grothe MJ, Utz L, Myers NE, Yakushev I, Grimmer T, Scherr M, Sorg C (2017) Individual correspondence of amyloid-beta and intrinsic connectivity in the posterior default mode network across stages of Alzheimer's disease. *J Alzheimers Dis* **58**, 763-773.

[72] Drzezga A, Becker JA, Van Dijk KR, Sreenivasan A, Talukdar T, Sullivan C, Schultz AP, Sepulcre J, Putcha D, Greve D, Johnson KA, Sperling RA (2011) Neuronal dysfunction and disconnection of cortical hubs in non-demented subjects with elevated amyloid burden. *Brain* **134**, 1635-1646.

[73] Elman JA, Madison CM, Baker SL, Vogel JW, Marks SM, Crowley S, O'Neil JP, Jagust WJ (2016) Effects of beta-amyloid on resting state functional connectivity within and between networks reflect known patterns of regional vulnerability. *Cereb Cortex* **26**, 695-707.

[74] Sheline YI, Raichle ME, Snyder AZ, Morris JC, Head D, Wang S, Mintun MA (2010) Amyloid plaques disrupt resting state default mode network connectivity in cognitively normal elderly. *Biol Psychiatry* **67**, 584-587.

[75] Pinheiroa L, Faustino C (2019) Therapeutic strategies targeting amyloid-beta in Alzheimer's disease. *Curr Alzheimer Res* **16**, 418-452.

[76] Reddy PH (2006) Amyloid precursor protein-mediated free radicals and oxidative damage: Implications for the development and progression of Alzheimer's disease. *J Neurochem* **96**, 1-13.

[77] Sorg C, Riedl V, Muhlau M, Calhoun VD, Eichele T, Laer L, Drzezga A, Forstl H, Kurz A, Zimmer C, Wohlschlager AM (2007) Selective changes of resting-state networks in

individuals at risk for Alzheimer's disease. *Proc Natl Acad Sci U S A* **104**, 18760-18765.

[78] Zhang Y, Simon-Vermot L, Araque Caballero MA, Gesierich B, Taylor ANW, Duering M, Dichgans M, Ewers M (2016) Enhanced resting-state functional connectivity between core memory-task activation peaks is associated with memory impairment in MCI. *Neurobiol Aging* **45**, 43-49.

[79] Ye Q, Su F, Shu H, Gong L, Xie C, Zhang Z, Bai F (2017) The apolipoprotein E gene affects the three-year trajectories of compensatory neural processes in the left-lateralized hippocampal network. *Brain Imaging Behav* **11**, 1446-1458.

[80] Machulda MM, Jones DT, Vemuri P, McDade E, Avula R, Przybelski S, Boeve BF, Knopman DS, Petersen RC, Jack CR, Jr. (2011) Effect of APOE epsilon4 status on intrinsic network connectivity in cognitively normal elderly subjects. *Arch Neurol* **68**, 1131-1136.

[81] Bonner-Jackson A, Okonkwo O, Tremont G (2012) Apolipoprotein E epsilon2 and functional decline in amnestic mild cognitive impairment and Alzheimer disease. *Am J Geriatr Psychiatry* **20**, 584-593.

[82] Bu G (2009) Apolipoprotein E and its receptors in Alzheimer's disease: Pathways, pathogenesis and therapy. *Nat Rev Neurosci* **10**, 333-344.

[83] Holtzman DM, Herz J, Bu G (2012) Apolipoprotein E and apolipoprotein E receptors: Normal biology and roles in Alzheimer disease. *Cold Spring Harb Perspect Med* **2**, a006312.

[84] Risacher SL, Kim S, Nho K, Foroud T, Shen L, Petersen RC, Jack CR, Jr., Beckett LA, Aisen PS, Koeppe RA, Jagust WJ, Shaw LM, Trojanowski JQ, Weiner MW, Saykin AJ, Alzheimer's Disease Neuroimaging Initiative (2015) APOE effect on Alzheimer's disease biomarkers in older adults with significant memory concern. *Alzheimers Dement* **11**, 1417-1429.

[85] Zhao N, Liu CC, Qiao W, Bu G (2018) Apolipoprotein E, receptors, and modulation of Alzheimer's disease. *Biol Psychiatry* **83**, 347-357.

[86] Michaelson DM (2014) APOE epsilon4: The most prevalent yet understudied risk factor for Alzheimer's disease. *Alzheimers Dement* **10**, 861-868.

[87] Wolk DA, Dickerson BC (2010) Apolipoprotein E (APOE) genotype has dissociable effects on memory and attentional-executive network function in Alzheimer's disease. *Proc Natl Acad Sci U S A* **107**, 10256-10261.

[88] Gong L, Shu H, He C, Ye Q, Bai F, Xie C, Zhang Z (2017) Convergent and divergent effects of apolipoprotein E epsilon4 and epsilon2 alleles on amygdala functional networks in nondemented older adults. *Neurobiol Aging* **54**, 31-39.

[89] Gong L, He C, Yin Y, Wang H, Ye Q, Bai F, Yuan Y, Zhang H, Lv L, Zhang H, Zhang Z, Xie C (2017) Mediating role of the reward network in the relationship between the dopamine multilocus genetic profile and depression. *Front Mol Neurosci* **10**, 292.

[90] He Y, Wang L, Zang Y, Tian L, Zhang X, Li K, Jiang T (2007) Regional coherence changes in the early stages of Alzheimer's disease: A combined structural and resting-state functional MRI study. *Neuroimage* **35**, 488-500.

[91] Yetkin FZ, Rosenberg RN, Weiner MF, Purdy PD, Cullum CM (2006) FMRI of working memory in patients with mild cognitive impairment and probable Alzheimer's disease. *Eur Radiol* **16**, 193-206.

[92] Teipel SJ, Bokde AL, Born C, Meindl T, Reiser M, Moller HJ, Hampel H (2007) Morphological substrate of face matching in healthy ageing and mild cognitive impairment: A combined MRI-fMRI study. *Brain* **130**, 1745-1758.

[93] Tsao DY, Schweers N, Moeller S, Freiwald WA (2008) Patches of face-selective cortex in the macaque frontal lobe. *Nat Neurosci* **11**, 877-879.

[94] Guillozet AL, Weintraub S, Mash DC, Mesulam MM (2003) Neurofibrillary tangles, amyloid, and memory in aging and mild cognitive impairment. *Arch Neurol* **60**, 729-736.

[95] Trojanowski JQ, Vandeerstichele H, Korecka M, Clark CM, Aisen PS, Petersen RC, Blennow K, Soares H, Simon A, Lewczuk P, Dean R, Siemers E, Potter WZ, Weiner MW, Jack CR, Jr., Jagust W, Toga AW, Lee VM, Shaw LM (2010) Update on the biomarker core of the Alzheimer's Disease Neuroimaging Initiative subjects. *Alzheimers Dement* **6**, 230-238.

[96] Davatzikos C, Xu F, An Y, Fan Y, Resnick SM (2009) Longitudinal progression of Alzheimer's-like patterns of atrophy in normal older adults: The SPARE-AD index. *Brain* **132**, 2026-2035.

[97] Da X, Toledo JB, Zee J, Wolk DA, Xie SX, Ou Y, Shacklett A, Parmpi P, Shaw L, Trojanowski JQ, Davatzikos C (2014) Integration and relative value of biomarkers for prediction of MCI to AD progression: Spatial patterns of brain atrophy, cognitive scores, APOE genotype and CSF biomarkers. *Neuroimage Clin* **4**, 164-173.

[98] Chen G, Ward BD, Xie C, Li W, Wu Z, Jones JL, Franczak M, Antuono P, Li SJ (2011) Classification of Alzheimer disease, mild cognitive impairment, and normal cognitive status with large-scale network analysis based on resting-state functional MR imaging. *Radiology* **259**, 213-221.

[99] Korthauer LE, Zhan L, Ajilore O, Leow A, Driscoll I (2018) Disrupted topology of the resting state structural connectome in middle-aged APOE epsilon4 carriers. *Neuroimage* **178**, 295-305.

[100] Wang X, Wang J, He Y, Li H, Yuan H, Evans A, Yu X, He Y, Wang H (2015) Apolipoprotein E epsilon4 modulates cognitive profiles, hippocampal volume, and resting-state functional connectivity in Alzheimer's disease. *J Alzheimers Dis* **45**, 781-795.

[101] Wang J, Wang X, He Y, Yu X, Wang H, He Y (2015) Apolipoprotein E epsilon4 modulates functional brain connectome in Alzheimer's disease. *Hum Brain Mapp* **36**, 1828-1846.

[102] Dragomir A, Vrahatis AG, Bezerianos A (2019) A network-based perspective in Alzheimer's disease: Current state and an integrative framework. *IEEE J Biomed Health Inform* **23**, 14-25.

[103] Pietrzak K, Czarnecka K, Mikiciuk-Olasik E, Szymanski P (2018) New perspectives of Alzheimer disease diagnosis - the most popular and future methods. *Med Chem* **14**, 34-43.

[104] Crosson B, Ford A, McGregor KM, Meinzer M, Cheshkov S, Li X, Walker-Batson D, Briggs RW (2010) Functional imaging and related techniques: An introduction for rehabilitation researchers. *J Rehabil Res Dev* **47**, vii-xxxiv.

[105] Salmon E, Bernard Ir C, Hustinx R (2015) Pitfalls and limitations of PET/CT in brain imaging. *Semin Nucl Med* **45**, 541-551.

[106] Bayram E, Caldwell JZK, Banks SJ (2018) Current understanding of magnetic resonance imaging biomarkers and

memory in Alzheimer's disease. *Alzheimers Dement (N Y)*
4, 395-413.

[107] Fehlbaum-Beurdeley P, Jarrige-Le Prado AC, Pallares D,
Carriere J, Guihal C, Soucaille C, Rouet F, Drouin D, Sol
O, Jordan H, Wu D, Lei L, Einstein R, Schweighoffer F,
Bracco L (2010) Toward an Alzheimer's disease diagno-
sis via high-resolution blood gene expression. *Alzheimers
Dement* **6**, 25-38.

[108] Henriksen K, O'Bryant SE, Hampel H, Trojanowski
JQ, Montine TJ, Jeromin A, Blennow K, Lonneborg A,
Wyss-Coray T, Soares H, Bazenet C, Sjogren M, Hu
W, Lovestone S, Karsdal MA, Weiner MW (2014) The
future of blood-based biomarkers for Alzheimer's disease.
Alzheimers Dement **10**, 115-131.

[109] Snyder HM, Carrillo MC, Grodstein F, Henriksen K,
Jeromin A, Lovestone S, Mielke MM, O'Bryant S, Sarasa

M, Sjogren M, Soares H, Teeling J, Trushina E, Ward
M, West T, Bain LJ, Shineman DW, Weiner M, Fillit
HM (2014) Developing novel blood-based biomarkers for
Alzheimer's disease. *Alzheimers Dement* **10**, 109-114.

[110] Zhang Z, Deng L, Bai F, Shi Y, Yu H, Yuan Y, Wang
K, Jiang T, Jia J, Zhang Z (2010) Alteration of resting
brain function by genetic variation in angiotensin convert-
ing enzyme in amnestic-type mild cognitive impairment
of Chinese Han. *Behav Brain Res* **208**, 619-625.

[111] Bai F, Shi Y, Yuan Y, Yue C, Zhuang L, Xu X, Liu X,
Zhang Z (2012) Association of a GSK-3beta polymor-
phism with brain resting-state function in amnestic-type
mild cognitive impairment. *J Alzheimers Dis* **32**, 387-396.