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ORIGINAL RESEARCH

APOE ε4 and cognitive reserve effects on the functional network in the Alzheimer's disease spectrum

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Abstract

The apolipoprotein E (*APOE*) ε4 allele is a genetic risk factor for Alzheimer's disease, whereas educational attainments have protective effects against cognitive decline in aging and patients with Alzheimer's disease. We examined the possible effects of years of education and *APOE* genotype on the topological properties of the functional network in normal aging, mild cognitive impairment and Alzheimer's disease. The years of education showed a significant, negative association with the local efficiency, clustering coefficient and small-worldness of functional networks in *APOE* ε4 noncarriers but not in ε4 carriers. These associations were mainly observed in normal aging and were reduced in mild cognitive impairment and Alzheimer's disease. Moreover, regions of the inferior frontal gyrus, temporal pole, and cuneus also showed correlations between education and nodal degree. Our findings demonstrated that the protective effects of education persist in *APOE* ε4 noncarriers but diminish in ε4 carriers. In addition, the protective effects of education were attenuated or reduced in the progression of Alzheimer's disease.

Keywords Education · fMRI · Functional connectivity · Alzheimer's disease · Graph theory

Introduction

Alzheimer's disease (AD), a progressive neurodegenerative disease associated with cognitive decline, is the most common form of dementia in the elderly population (Masters et al. 2015). Mild cognitive impairment (MCI) is a transitional stage between normal aging and AD and is considered a prodromal phase of AD (Albert et al. 2011) with a high risk of dementia.

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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Previous studies have found that risk factors of AD range from genetics to environmental influences (Masters et al. 2015; Reitz and Mayeux 2014). Among these factors, the apolipoprotein E (*APOE*) ε4 allele is the most relevant genetic risk factor for AD (Farrer et al. 1997; Karch and Goate 2015; Reitz and Mayeux 2014). There exist three major polymorphic *APOE* alleles (ε2, ε3 and ε4) on chromosome 19, corresponding to 6 phenotypes (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4 and ε4/ε4) (Farrer et al. 1997; Liu et al. 2013) in humans. Individuals who carry at least one *APOE* ε4 allele (including ε2/ε4, ε3/ε4 and ε4/ε4) exhibit an increased risk and an earlier age at onset of AD compared with noncarriers (Albert et al. 2011; Liu et al. 2013). *APOE* gene regulates amyloid β (Aβ) oligomerization and aggregation in the brain (Karch and Goate 2015). Previous studies have found that compared with *APOE* ε4 noncarriers, ε4 carriers exhibit greater Aβ deposition during normal aging, MCI and AD (Farlow et al. 2004; Honea et al. 2009; Jack et al. 2015; Liu et al. 2013). Furthermore, the *APOE* in human cerebrospinal fluid was found to bind specifically to immobilized Aβ peptide (Selkoe 2005). These results established a link between *APOE* ε4 and increased risk of Aβ. In turn, Aβ deposition may result in more severe brain atrophy, especially around the medial temporal lobe (den Heijer et al. 2002; Manning et al. 2014), and increase the risk of cognitive impairment and dementia (Jack et al. 2015). Thus, this risk-related polymorphism has been proposed as a potential target for the identification of individuals at higher risk of developing dementia (Wolk and Mahley 2010).

The *APOE* ε4 genotype is one of the multiple factors that may affect the progression of AD. Additionally, educational attainment plays an important role in aging and has been related to the concept of cognitive reserve. Cognitive reserve refers to the brain's ability to use pre-existing cognitive-processing approaches or compensatory mechanisms when coping with brain pathology or during the execution of cognitive tasks (Stern 2009). Epidemiological studies suggest that lifestyle factors, including educational and occupational attainment, leisure activities, and intelligence quotient (IQ) (Martinez et al. 2018; Stern 2009), can increase cognitive reserve and protect against cognitive decline and brain atrophy during healthy aging (Arenaza-Urquijo et al. 2013; Mungas et al. 2018; Posner and Rothbart 2005; Stern 2012; Tucker and Stern 2011) and AD (Amieva et al. 2014; Scarmeas et al. 2003; Xu et al. 2016). Educational attainment is one of the most studied proxy measures of cognitive reserve and can shape the neural networks of the brain (Arenaza-Urquijo et al. 2013; Barulli and Stern 2013; Cheng 2016; Marques et al. 2016; Perry et al. 2017; Posner and Rothbart 2005; Stern 2006). The dementia risk was reduced by increasing education (Xu et al. 2016), and education could provide protection against cognitive decline until the pathology of AD became more severe (Amieva et al. 2014; Franzmeier et al. 2017; Xu et al. 2016). The protective role of education against age-related or pathological changes in cognition has also been documented by neuroimaging studies. For example, individuals with higher education have a greater capacity to counteract impacts on gray matter integrity and cortical thickness in normal aging, MCI and AD (Franzmeier et al. 2018; Liu et al. 2012; Serra et al. 2011; Stern 2012). In addition, studies investigating pathophysiological markers have found that higher levels of education are associated with a greater inhibitory effect against Aβ deposition before the preclinical stage (Arenaza-Urquijo et al. 2017; Yasuno et al. 2015).

Otherwise, the role of genotype-by-education interactions for cognitive function has gained interest. For example, researchers investigated the interaction effects between the Short Portable Mental Status Questionnaire scores and *APOE* genotype from the MacArthur Study of Successful Aging and observed a reduced protective effects of education in *APOE* ε4 carriers (Seeman et al. 2005). Also, the protective effects of education were attenuated or reduced in *APOE* ε4 carriers of normal aging, which may be correlated with the rapid decline in cognitive performance (López et al. 2018; Winnock et al. 2002). These findings suggest that both the education and *APOE* ε4 appear to be associated with cognitive performance via different neuropsychological tests.

In additional to measuring the neuropsychological tests, recent developments in the analysis of complex networks with graph theory have enabled the quantitative characterization of the topological properties of brain networks (Bullmore and Sporns 2009; Deco et al. 2015; Sporns 2011; Yan et al. 2019). Previous studies have found that small-worldness topologies are disrupted in both MCI and AD patients (Vecchio et al. 2014; Wang et al. 2016; Zhao et al. 2012). In previous studies, using resting-state functional magnetic resonance imaging (fMRI), the *APOE* genotype has been found to modulate brain network properties (Zhao et al. 2012) and exhibit dissociable effects on memory and attentional-executive network in AD (Wolk and Mahley 2010). In addition, *APOE* ε4 allele genotype leads to distinct default mode network functional alterations (Chiesa et al. 2019). Moreover, a study investigating anatomical cortical networks observed that compared with noncarriers, *APOE* ε4 carriers exhibit a less optimal topological organization of brain networks with increased clustering coefficient and path lengths (Mohammed et al. 2015). In contrast to the deterioration effects, existing research suggests that education has obvious protective effects on brain networks (Arenaza-Urquijo et al. 2013; Franzmeier et al. 2017, 2018; Marques et al. 2016), including an association between higher education and greater functional connections and network efficiency (Marques et al. 2016). In other studies, cognitive reserve (measured as the years of education and IQ) was found to moderate the association between functional network and memory in MCI (Franzmeier et al. 2017). Furthermore, a magnetoencephalographic functional network study found a negative correlation between synchronization of

the whole network and cognitive reserve (Martinez et al. 2018). Consistent with previous studies (Franzmeier et al. 2018; López et al. 2018; Seeman et al. 2005), the *APOE* ε4 allele and years of education exhibited contrasting effects on brain networks, respectively. However, the mechanisms of functional brain networks that underlie these possible interactions between education and the *APOE* genotype remain largely unknown in the AD spectrum.

The Alzheimer's Disease Neuroimaging Initiative (ADNI) database is open and contains both APOE genotype and education information of the AD spectrum, which provides advantages to explore the potential mechanisms of the genotype, education, and genotype-by-education effects on the functional brain network properties. In the present study, we used the data from ADNI2 to explore the possible genotype-by-education effects on functional brain networks. The resting-state fMRI method and graph theoretical analysis were used to quantitatively characterize the topological properties of functional brain networks, including small-worldness properties, global and local efficiency, and nodal degree. Spearman correlation analysis was used to measure the associations between the years of education and network properties in different *APOE* states (*APOE* ε4 noncarriers and ε4 carriers) in the progression of AD (normal aging, MCI and AD). Furthermore, we examined the genotype, education, and genotype-by-education interaction differences by using an ANCOVA analysis among normal aging, MCI, and AD.

Methods

Participants

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). For up-to-date information, see www.adni-info.org.

Subjects of normal aging, MCI and AD from ADNI2 with initial or first screening visits were chosen in this study. Briefly, the normal aging group had no memory complaints and exhibited normal cognitive performance on the mini-mental state examination (MMSE); the MCI group had self-reported memory complaints, exhibited an MMSE total score greater than 24, and displayed preserved daily functioning, thus failing to meet the diagnostic criteria for AD. The clinical dementia rating (CDR) scores of normal aging, MCI and AD subjects were 0, 0.5 and 1, respectively. The ADNI2 collected blood samples for DNA and RNA extraction. *APOE* genotyping was performed on 85 genomic DNAs using the Illumina HumanOmniExpress BeadChip, which contains 730,525 SNP markers, according to the manufacturer's protocols. This study used baseline or screening data from cognitive assessments, including the functional activity questionnaire (FAQ), MMSE, geriatric depression scale (GDS), CDR and neuropsychiatric inventory questionnaire (NPI_Q).

In the present study, we selected the data of 110 participants, including 25 normal aging, 57 MCIs and 28 ADs. Also, there were 57 ε4 noncarriers (ε2/ε2, ε2/ε3 and ε3/ε3) and 53 ε4 carriers (ε2/ε4ε, 3/ε4 and ε4/ε4). Table 1 illustrates clinical assessments and demographic information, including subjects for whom fMRI data were acquired, and presents information regarding the *APOE* genotype and years of education.

Imaging acquisition

The functional and structural magnetic resonance imaging (MRI) data were both collected according to the ADNI acquisition protocol using three-Tesla (3 T) scanners. We used data only from the Philips scanner to ensure consistency of data acquisition parameters. High-resolution 3D T1-weighted MR images were acquired on a 3.0 T Philips scanner using the ADNI2 (8-channel coil, TR = 6.8 ms, TE =3.16 mm, flip-angle = 9°, slice thickness = 1.2 mm, resolution = 256 × 256 mm and FOV = 26 cm). The acquisition plane of MRI data was SAGITTAL plane. The resting-state fMRI data of each subject consisted of 140 functional volumes and were acquired using the following parameters: repetition time (TR) = 3000 ms; echo time (TE) = 30 ms; flip angle = 80°; slice thickness = 3.313 mm; and 48 slices. All subjects were instructed to keep their eyes closed but not fall asleep, relax their minds, and move as little as possible during the data acquisition.

Data prepocessing

The data preprocessing was conducted using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) and the Data Processing Assistant for Resting-State fMRI (DPARSF, http://www.restfmri.net/forum/dparsf). For each run, the first ten time points were discarded to account for signal equilibrium and the adaptation of participants to the circumstances. The remaining functional images were first corrected for timing and then realigned to the first volume to correct for head motion, which did not exceed 2.0 mm of displacement or 2.0° of rotation in any direction in any subject. Subsequently, the functional images were spatially normalized to the Montreal Neurological Institute (MNI) template and resampled to a voxel size of $3 \times 3 \times 3$ mm^3. Then, temporal bandpass filtering ($0.01\ \text{Hz} \le f \le 0.1\ \text{Hz}$) was performed to reduce the effects of low-frequency drift and high-frequency

Table 1 Demographic and clinical characteristics of the samples[a]

Measure	Normal Aging		MCI		AD		*P* value[b]		
	ε4-	ε4+	ε4-	ε4+	ε4-	ε4+	Diag	Gene	Inter
Demographics									
Number	16	9	34	23	7	21	0.004[c]	–	–
Age	76(7)	72(5)	72(8)	72(5)	68(7)	74(7)	0.31	0.70	0.11
Education	16(2)	17(2)	16(2)	16(3)	16(3)	15(3)	0.25	0.88	0.46
Gender (M/F)	8/8	2/7	20/14	12/11	3/4	14/7	0.28	0.87	–
General cognition									
FAQ	0.3(0.6)	0.0(0.0)	3.0(3.6)	5.0(5.9)	16(9.7)	15(7.0)	<0.001	0.78	0.49
MMSE	29(1.1)	29(1.7)	28(1.6)	27(1.9)	22(2.4)	23(2.5)	<0.001	0.52	0.06
GDS	0.4(0.6)	0.6(1.1)	1.6(1.5)	2.1(1.9)	1.7(1.6)	1.5(1.0)	0.001	0.64	0.60
CDR	0.0(0.0)	0.0(0.0)	0.5(0.1)	0.5(0.0)	0.9(0.2)	0.8(0.2)	<0.001	0.92	0.85
NPI_Q	1.0(1.7)	0.3(0.5)	2.5(3.2)	3.6(3.5)	4.1(4.7)	3.8(3.9)	0.002	0.98	0.46

Abbreviations: *MCI* mild cognitive impairment, *AD* Alzheimer's disease, *ε4- APOE* ε4 noncarriers, *ε4+ APOE* ε4 carriers, *FAQ* functional activity questionnaire, *MMSE* mini-mental state examination, *GDS* geriatric depression scale, *CDR* clinical dementia rating, *NPI_Q* neuropsychiatric inventory questionnaire

[a] Data are expressed as the mean (SD)

[b] *P* value was obtained via a two-way analysis of covariance (ANCOVA)

[c] The χ^2 test was used to analyze *APOE* percentage difference among normal aging, MCI and AD

noise. To reduce the effects of motion and nonneuronal blood oxygen level-dependent (BOLD) fluctuations, head motion, the cerebrospinal fluid (CSF) signal and white matter signals were further removed as nuisance covariates (Seeman et al. 2005). Finally, the fMRI images were smoothed using a Gaussian filter with a full width at half maximum (FWHM) of 4 mm.

Construction of functional brain network

After data preprocessing, regions based on the anatomical automatic labeling (AAL; http://www.cyceron.fr/freeware/) (Tzourio-Mazoyer et al. 2002) brain template were extracted per subject. The AAL brain template contains 90 regions of cerebrum and 26 regions of cerebellum. In this study, we focused on brain network analysis of the cerebrum. The fMRI time series was computed in each of 90 regions by averaging all voxels within each region at each time point in the time series, resulting in 130 time points with 90 anatomical regions for each subject. Then, these time series were used to construct a 90-node whole-brain functional connectivity network by calculating the Pearson correlation coefficient in the residual time courses between each pair of regions of interest (ROIs), and then a 90×90 correlation matrix was obtained for each subject. Finally, each correlation matrix was repeatedly thresholded into a binarized matrix with a wide range of sparsity (10% to 40%) with intervals of 0.01. Through this threshold, unweighted graphs were obtained in which the nodes represent the brain regions and the edges represent the functional relationships between brain regions. Further network analysis was based on the 90×90 binarized matrixes of each subject.

Graph theory analysis of functional brain network

Graph theory analysis was performed by using GRETNA software (http://www.nitrc.org/projects/gretna/). The network architecture was investigated at both global and regional levels in the constructed resting-state functional brain networks. Compared with random networks, small-worldness was originally proposed by Watts and Strogatz to have higher local clustering and equivalent characteristic path length. In this work, we calculated the small-worldness of the binarized brain networks with a wide range of sparsity (Tzourio-Mazoyer et al. 2002). The seven network matrixes were adopted to characterize the global topological organization of the brain networks, including clustering coefficient, Cp (representing that neighbors of the node are also neighbors each other); characteristic path length, Lp (representing the average of the shortest path lengths of all the nodes in the network); normalized clustering coefficient, γ; normalized characteristic path length, λ; small-worldness, sigma, $\sigma = \gamma/\lambda$ (representing the functional integration and segregation); global efficiency, Eg (representing the functional integration of a network); and local efficiency, Eloc (a measure of the functional segregation). Typically, to diagnose small-worldness properties, the characteristic path length and clustering coefficient were compared with corresponding values

(C_{random}, L_{random}) and averaged across 100 random networks with the same number of nodes and degree distribution. Small-worldness is characterized by a high normalized clustering coefficient γ (Cp/C_{random}) > 1 and low normalized characteristic path length λ (Lp/L_{random}) ~ 1 compared to random networks. Thus, the value of small-worldness is greater than 1. Simply, the topological properties of Lp, λ and Eg are considered measures of functional integration. The high Eg represents the strong ability of parallel information transfer in the network. The abilities of segregation and error tolerance of a network can be expressed as Cp, γ and Eloc. A network with high Eloc shows good robustness to the deletion of individual nodes. Moreover, the nodal degree was computed to examine the regional characteristics of each cortical region in the functional networks (Watts and Strogatz 1998). Here, we provide an overview of definitions and brief interpretations of the parameters (Supplementary Table 1).

Statistical analysis

All statistical analyses were performed using SPSS 19 software (SPSS, Inc., Chicago, IL). The age, years of education and clinical information were compared using a two-way analysis of variance (ANOVA) with factors of genotype (*APOE* ε4 carriers and noncarriers) and diagnosis (normal aging, MCI and AD). The gender was analyzed using a χ^2 test. The χ^2 test was also used to analyze *APOE* percentage differences among normal aging, MCI and AD. The results were considered significant at the level of $P < 0.05$.

Spearman correlation was used to analyze associations between the years of education and network properties. The correlation results of nodal degree were then corrected by false discovery rate (FDR, $P < 0.05$). If any significant correlations were observed between education and properties, a two-way analysis of covariance (ANCOVA) was used to determine the genotype, education, and genotype-by-education interaction differences with the factor of genotype (*APOE* ε4 carriers and noncarriers) and covariates of the years of education, gender, and age. Furthermore, we determined the genotype, education and interaction effects on these significant interacting properties among normal aging, MCI, and AD.

Results

Demographic and neuropsychological variables

The effects of diagnosis and *APOE* ε4 carrier status on the demographics and clinical performances are presented in Table 1. The six subgroups did not differ in age, education or gender (all $P > 0.05$). The *APOE* ε4 percentage differed among NC, MCI and AD ($P = 0.004$), consistent with a high genetic risk at onset of AD in *APOE* ε4 carriers (Farrer et al. 1997; Liu et al. 2013). Unsurprisingly, the clinical and neuropsychological test performances significantly differed among the diagnostic groups (all $P < 0.005$). No significant effect of the *APOE* genotype or interaction effect was observed on any cognitive measure.

Relationships between the years of education and global properties

We found that the years of education were significantly, negatively correlated with the local efficiency (Eloc), clustering coefficient (Cp), normalized clustering coefficient (γ) and small-worldness (σ) (Fig. 1, all $P < 0.05$) by using Spearman correlation analysis. However, these correlations were absent in *APOE* ε4 carriers (Fig. 1a, Fig. 2). We further investigated the heterogeneity of the association in the normal aging, MCI and AD groups. In *APOE* ε4 noncarriers, significant educational correlations on the normalized clustering coefficient and small-worldness (all $P < 0.05$) were observed in normal aging and MCI groups and local efficiency in normal aging (Fig. 1b).

To determine educational effects in detail, a two-way ANCOVA was used to determine the main effects of genotype and education and genotype-by-education interaction differences in significantly correlated properties via Spearman correlation. As shown in Table 2, we found significant differences based on education in the normalized clustering coefficient (γ, $F = 7.169$, $P = 0.009$), small-worldness (σ, $F = 6.497$, $P = 0.012$), and local efficiency (Eloc, $F = 4.018$, $P = 0.048$). Additionally, significant genotype differences were observed in the normalized clustering coefficient (γ, $F = 4.271$, $P = 0.041$) and small-worldness (σ, $F = 5.930$, $P = 0.017$). Moreover, significant interaction effects were found in the normalized clustering coefficient (γ, $F = 5.349$, $P = 0.023$) and small-worldness (σ, $F = 7.187$, $P = 0.009$). The local efficiency (Eloc, $F = 2.871$, $P = 0.093$) showed a marginally significant effect, but the effect of the clustering coefficient was not significant. Furthermore, we determined interaction differences in the normalized clustering coefficient, small-worldness, and local efficiency among normal aging, MCI and AD, respectively (Fig. 2). However, no interaction effect was observed in any group (all $P > 0.05$).

Relationships between the years of education and nodal properties

Through a Spearman correlation analysis, we found significant correlations between the years of education and nodal degree in the noncarriers but not in the carriers (Table 3). As shown in Fig. 3 and Fig. 4, significant, negative correlations were observed in seven regions predominantly located in the left orbital part of the inferior frontal gyrus [ORBinf], the bilateral parahippocampal gyrus [PHG], the left amygdala

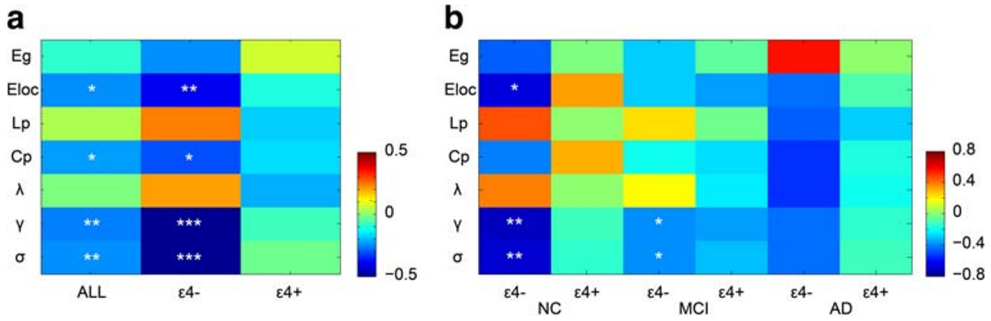

Fig. 1 Results of the Spearman correlation between education and global properties. The threshold value for establishing significance was set at $P < 0.05$. (**a**) Results of the Spearman correlation between education and global properties in *APOE* ε4 noncarriers and carriers. (**b**) The associations in the normal aging, MCI and AD among the *APOE* ε4 noncarriers and *APOE* ε4 carriers. The color bar shown in **a** and **b** represents the correction coefficient. Abbreviations: ε4-, *APOE* ε4 noncarriers; ε4+, *APOE* ε4 carriers; *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$; MCI, mild cognitive impairment; AD, Alzheimer's disease

[AMYG], the right superior temporal gyrus (temporal) [TPOsup] and the bilateral middle temporal pole (temporal) [TPOmid] (all $P < 0.05$, FDR-corrected). Furthermore, in normal aging, the years of education was significantly and negatively correlated with the nodal degree in the regions of the AMYG.L, TPOsup.R and TPOmid.R. Moreover, MCI patients showed significant and negative correlations in the PHG.L and TPOmid.R. Additionally, the bilateral cuneus [CUN] regions showed significant and positive correlations between education and the nodal degree (both $P < 0.05$, FDR-corrected).

Using ANCOVA, we further investigated the genotype, education, and genotype-by-education effects on nodal degree in these significantly correlated nine regions. As shown in Table 4, most regions (eight-ninths) exhibited significant education differences. Significant genotype differences were observed in the bilateral CUN, TPOsup.R, and TPOmid.R (all $P < 0.015$). Additionally, significant interaction effects were observed in the CUN.L ($F = 7.347$, $P = 0.008$), CUN.R ($F = 6.978$, $P = 0.010$), TPOsup.R ($F = 6.758$, $P = 0.011$), and TPOmid.R ($F = 9.033$, $P = 0.003$). Moreover, we determined interaction differences on nodal degree in the bilateral CUN, TPOsup.R, and TPOmid.R among normal aging, MCI and AD, respectively (Fig. 4). Furthermore, TPOmid.R showed a significant interaction effect in normal aging ($F = 4.303$, $P = 0.052$). No interaction effect was observed in MCI and AD.

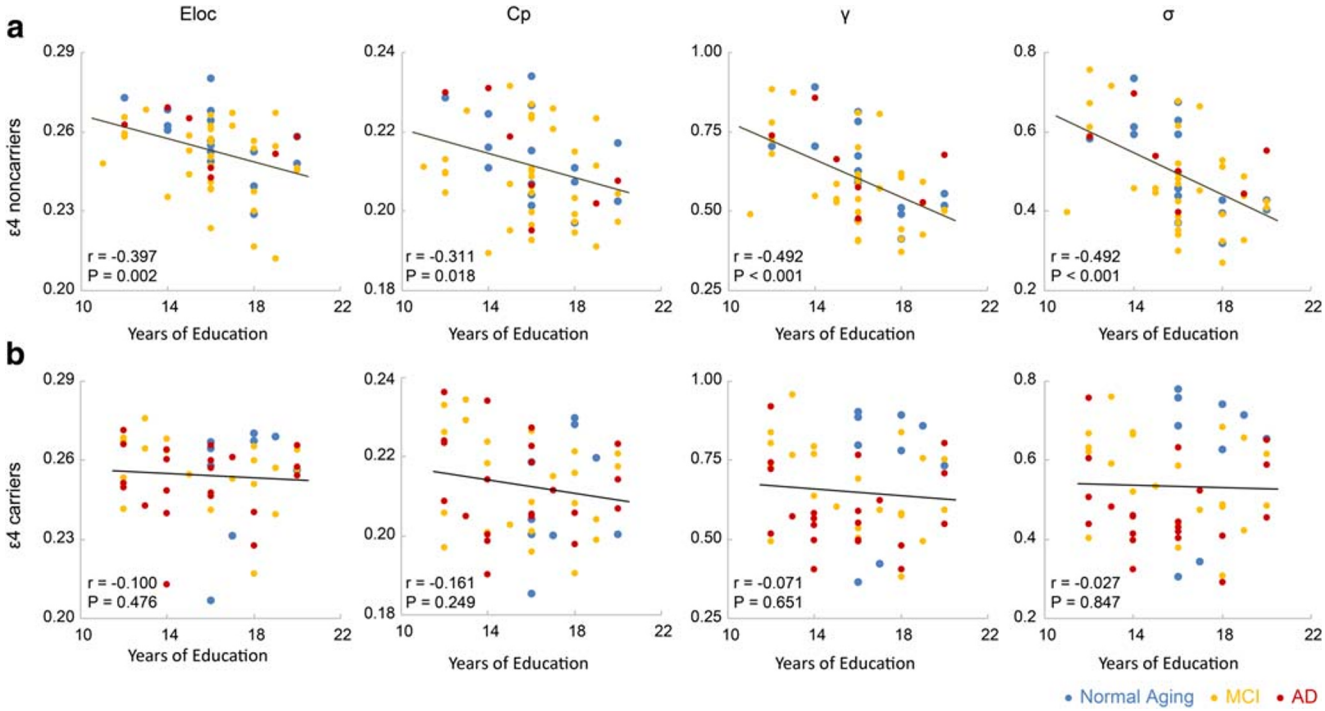

Fig. 2 Scatter plots of the Spearman correlation between education and global properties among the normal aging, MCI and AD. (**a**) Correlation results in the *APOE* ε4 noncarriers. (**b**) Correlation results in the *APOE* ε4 carriers. Note: Blue: Normal Aging; Yellow: MCI, mild cognitive impairment; Red: AD, Alzheimer's disease. r, Spearman correlation coefficient; P, *P* value (FDR-corrected)

Table 2 Education and *APOE* Genotype effects on global properties

Matrixes	Education effects F (*P* value)	*APOE* genotype F (P value)	Genotype-by-education Interaction F (P value)
Eloc	**4.018(0.048)**	2.674(0.105)	2.871(0.093)
Cp	3.240(0.075)	0.641(0.425)	0.686(0.410)
γ	**7.169(0.009)**	**4.271(0.041)**	**5.349(0.023)**
σ	**6.497(0.012)**	**5.930(0.017)**	**7.187(0.009)**

Note: bold figures indicate $P < 0.05$. *P* value was obtained via a two-way analysis of covariance (ANCOVA) with covariates of the years of education, gender, and age

Abbreviations: *Eloc* local efficiency, *Cp* clustering coefficient, γ normalized clustering coefficient, σ small-worldness

Discussion

We examined the resting-state functional network among individuals in normal aging, MCI and AD groups to evaluate the effects of *APOE* genotype and the years of education on functional brain networks. In *APOE* ε4 noncarriers, the years of education were significantly, negatively associated with the local efficiency, clustering coefficient, normalized clustering coefficient, and small-worldness. Such associations reflect the protective effects of education attainment. We further found significant nodal degree correlations in brain regions mainly located in the orbital part of the inferior frontal gyrus, temporal pole and cuneus in *APOE* ε4 noncarriers in the normal aging and MCI groups, especially the normal aging group. Furthermore, property-related results were supported by significant genotype-by-education interaction differences via ANCOVA. In addition, interactions were found especially in normal aging. Therefore, there are levels of protective effects of education in the progression of AD, but they are greatly affected by the presence of *APOE* ε4.

Years of education altered the global topologies of functional network

The small-worldness topology is a fundamental principle of the structural and functional organization of complex brain

Table 3 Results of the Spearman correlation between education and nodal degree

	ALL		Normal Aging		MCI		AD	
	r	P	r	P	r	P	r	P
APOE ε4-								
ORBinf.L	**−0.42**	**0.024**	−0.36	0.438	−0.38	0.186	−0.81	0.991
PHG.L	**−0.40**	**0.026**	−0.16	0.764	**−0.53**	**0.036**	−0.20	0.991
PHG.R	**−0.39**	**0.027**	−0.51	0.238	−0.43	0.095	−0.20	0.991
AMYG.L	**−0.42**	**0.026**	**−0.72**	**0.049**	−0.30	0.249	−0.40	0.991
TPOsup.R	**−0.39**	**0.027**	**−0.80**	**0.018**	−0.26	0.341	−0.20	0.991
TPOmid.L	**−0.49**	**0.005**	−0.38	0.413	−0.45	0.081	−0.78	0.991
TPOmid.R	**−0.60**	**<0.001**	**−0.73**	**0.045**	**−0.55**	**0.031**	−0.49	0.991
CUN.L	**0.41**	**0.020**	0.55	0.202	0.37	0.183	0.23	0.991
CUN.R	**0.47**	**0.007**	0.46	0.300	0.46	0.089	0.72	0.991
APOE ε4+								
ORBinf.L	−0.14	0.892	0.41	0.969	−0.11	0.876	−0.29	0.962
PHG.L	−0.31	0.769	−0.57	0.969	−0.40	0.545	−0.22	0.981
PHG.R	−0.26	0.720	−0.30	0.969	−0.44	0.545	−0.16	0.981
AMYG.L	−0.03	0.953	−0.21	0.969	−0.28	0.685	0.20	0.981
TPOsup.R	0.10	0.860	0.17	0.969	−0.09	0.896	0.32	0.962
TPOmid.L	−0.22	0.844	−0.23	0.969	−0.19	0.770	−0.33	0.962
TPOmid.R	−0.20	0.884	0.37	0.969	−0.47	0.495	−0.13	0.981
CUN.L	0.01	0.977	−0.07	0.969	−0.03	0.941	0.06	0.981
CUN.R	0.01	0.999	0.64	0.969	−0.04	0.941	0.12	0.981

Abbreviations: *MCI* mild cognitive impairment, *AD* Alzheimer's disease, *ε4- APOE* ε4 noncarriers, *ε4+ APOE* ε4 carriers, *r* Spearman correlation coefficient; *P P* value (FDR-corrected). Note: bold figures indicate $P < 0.05$

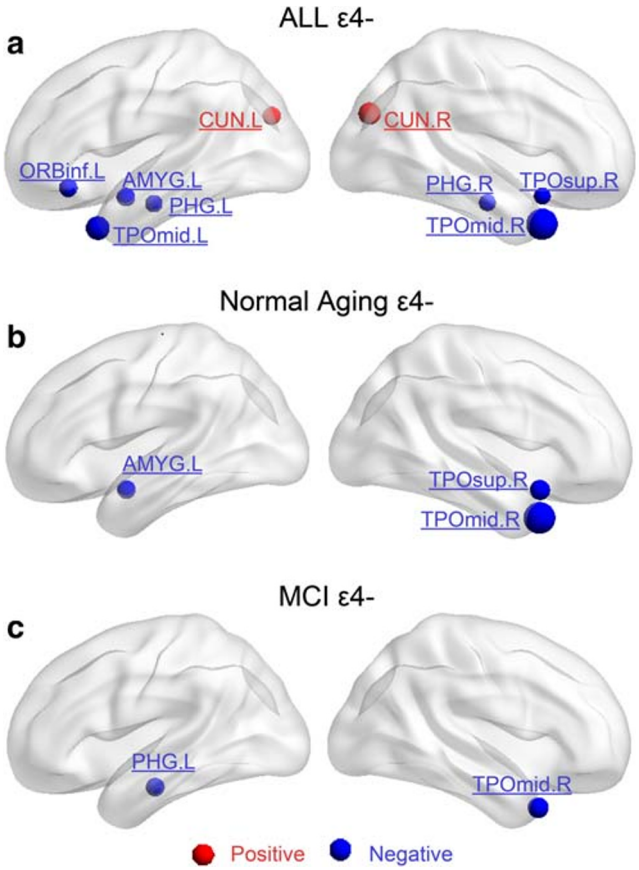

Fig. 3 Plots of regions on the cortical surface with significant associations between education and the nodal degree on the cortical surface of the *APOE* ε4 noncarriers. The threshold was $P < 0.05$, FDR-corrected. Significantly associated regions in all individuals (**a**), Normal Aging (**b**), and MCI patients (**c**). There was no such correlation in the *APOE* ε4 noncarriers with AD and the *APOE* ε4 carriers. The spheres in red indicate positive correlations between education and nodal degree, and those in blue indicate negative correlations. The size of the spheres indicates the correlation coefficient. Nodes are mapped onto cortical surfaces using BrainNet Viewer software (Xia et al. 2013). Abbreviations: ε4-, *APOE* ε4 noncarriers; ε4+, *APOE* ε4 carriers; MCI, mild cognitive impairment; AD, Alzheimer's disease

networks that has greatly impacted studies investigating topological architectures using a systematic perspective in healthy and diseased populations (Bullmore and Sporns 2009; Sporns 2011). The well-known small-worldness topology refers to a large number of spatially distributed network communities (integration) with high computations in clustered connectivity (segregation). In addition, the topological properties of the characteristic path length, normalized characteristic path length and global efficiency represent the global integration of a network. Moreover, the clustering coefficient, normalized clustering coefficient and local efficiency are regarded as measures of the segregation and error tolerance of a network. Small-worldness presents a balance between integration and segregation, thus representing information processing (Bullmore and Sporns 2009; Deco et al. 2015; Sporns 2011).

Education is considered a proxy measure of cognitive reserve that affects the structural and neural networks of the brain (Barulli and Stern 2013; Perry et al. 2017; Posner and Rothbart 2005; Stern 2006). Consistent with this notion, in this study, the results of a negative association between higher years of education and lower clustering coefficient, normalized clustering coefficient and small-worldness reflected a decreased segregation of the functional network and reinforced the fine balance between segregation and integration. However, inconsistent with the present results, certain previous studies have reported a higher increase in the local efficiency and clustering coefficient in individuals with higher education levels (Marques et al. 2016; Marques et al. 2015). This inconsistency is most likely because the years of education differed among the subjects. Recently, Lenehan et al. (2015) reviewed education moderations and found little consistent evidence to support the assumption of the cognitive reserve, and the effect of education was restricted to particular subgroups or certain cognitive functions. Specifically, we should consider that the educational years (with a mean of 16 years) of the participants in the present study were considerably greater than those in former studies (with a mean of 5.37 years) (Lenehan et al. 2015; Marques et al. 2015). Consequently, the potential protective effects of education were no longer evident as the education level increases beyond the 8-year threshold (Lyketsos et al. 1999; Zahodne et al. 2015). Zahodne et al. (2015) proposed that early education (i.e., up to 8 years) may promote aspects of development during a sensitive period in childhood, which protects against late-life cognitive decline. In contrast, subjects with a higher level of education (i.e., 9 years and beyond) showed multiple pathways that influenced brain function (Joo et al. 2017). A 20-year longitudinal study suggested that the initial decline in cognition is associated with the immediate decline in dementia in the lower-level education group. However, higher-level education protects against further cognitive decline for approximately 7 years until the pathology becomes more severe (Amieva et al. 2014). These findings suggest that dimorphism exists in the educational effects on cognition reserve. Combined with our findings and previous reports, we suggest a novel protective effect of education on functional networks and cognition for these individuals with higher-level education.

Effects of interaction between genotype and education on global topologies

The dysfunction of functional network association in carriers of *APOE* ε4 has been previously demonstrated (Wang et al. 2015; Wolk and Mahley 2010; Zhao et al. 2012). However, to the best of our knowledge, our study is the first to investigate the effects of *APOE* ε4 and protective educational attainment on network properties by using

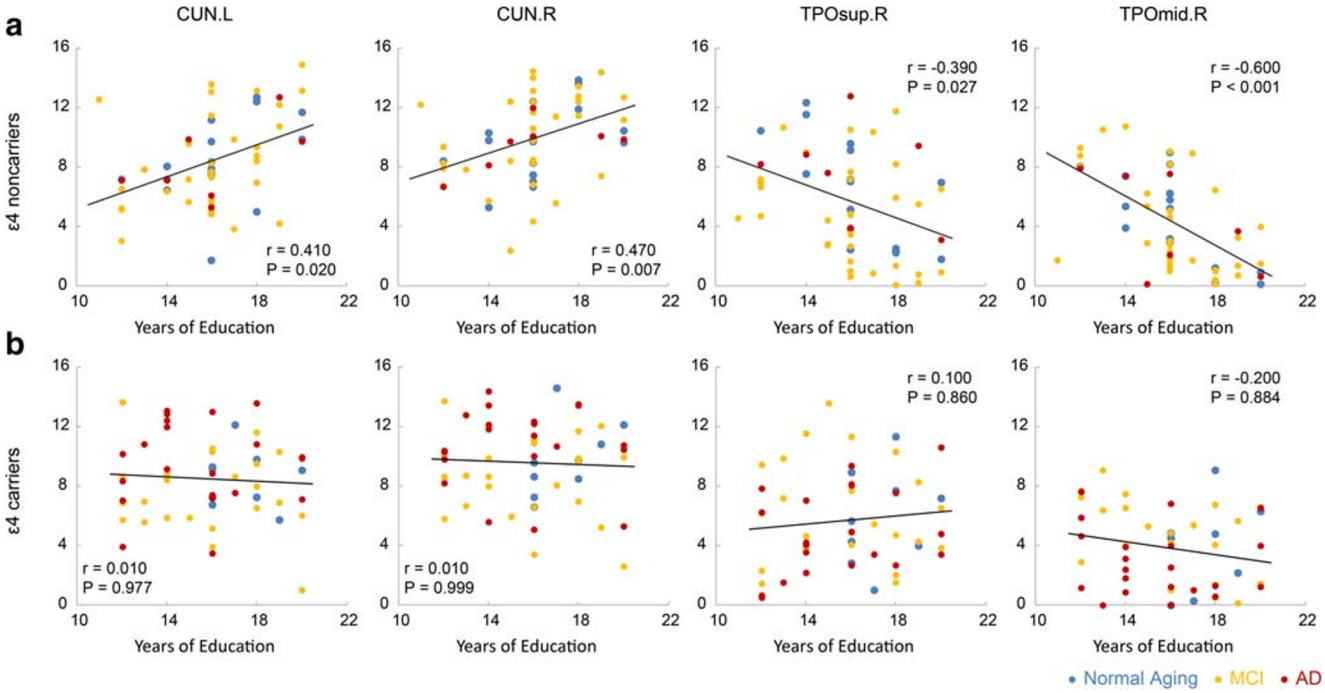

Fig. 4 Scatter plots of the Spearman correlation between education and nodal degree among the normal aging, MCI and AD. We found nine educational correlated regions in nodal degree (Fig. 3a). Here, we only present four regions that observed significant genotype-by-education interaction effects among these nine regions via ANCOVA. Note: Blue: Normal Aging; Yellow: MCI, mild cognitive impairment; Red: AD, Alzheimer's disease. r, Spearman correlation coefficient; P, *P* value (FDR-corrected)

fMRI. Significant associations were observed between the years of education and the local efficiency, clustering coefficient, normalized clustering coefficient and small-worldness in the *APOE* ε4 noncarriers, particularly in the normal aging and MCI groups, whereas such associations were absent in the ε4 carriers (Fig. 1). As mentioned above, correlated results indicated that *APOE* ε4 noncarriers with higher education showed lower local efficiency, clustering coefficient, normalized clustering coefficient and small-worldness, suggesting lower segregation of functional networks and reinforcement of the fine balance between segregation and integration. Moreover, these protective effects of education were reduced or absent in ε4 carriers, which may caused by severe brain atrophy (den Heijer et al. 2002; Manning et al. 2014) and dysfunction in functional networks with an increased clustering coefficient in carriers (Mohammed et al. 2015; Wang et al. 2015; Wolk and Mahley 2010; Zhao et al. 2012).

Table 4 Education and *APOE* Genotype effects on nodal degree

Matrixes	Education effects F (P value)	*APOE* genotype F (P value)	Genotype-by-education Interaction F (P value)
ORBinf.L	**5.563(0.020)**	1.506(0.223)	1.943(0.166)
PHG.L	**12.181(0.001)**	1.203(0.275)	1.097(0.297)
PHG.R	**10.859(0.001)**	1.468(0.228)	1.389(0.241)
AMYG.L	**8.453(0.004)**	3.682(0.058)	3.492(0.064)
TPOsup.R	2.785(0.098)	**6.585(0.012)**	**6.758(0.011)**
TPOmid.L	**11.85(0.001)**	3.265(0.074)	3.440(0.066)
TPOmid.R	**22.551(<0.001)**	**9.921(0.002)**	**9.033(0.003)**
CUN.L	**5.956(0.016)**	**7.248(0.008)**	**7.347(0.008)**
CUN.R	**4.414(0.038)**	**6.397(0.013)**	**6.978(0.010)**

Note: bold figures indicate $P < 0.05$. *P* value was obtained via a two-way analysis of covariance (ANCOVA) with covariates of the years of education, gender, and age

Abbreviations: *ORBinf.L* the left orbital part of the inferior frontal gyrus, *PHG* the bilateral parahippocampal gyrus, *AMYG.L*, the left amygdala, *TPOsup.R* the right superior temporal gyrus (temporal), *TPOmid* the bilateral middle temporal pole (temporal), *CUN* the bilateral cuneus

We propose two reasonable explanations for these protective effects in *APOE* ε4 noncarriers. On the one hand, the *APOE* ε4 allele has been shown to inhibit neuronal growth, survival, branching and extension in both in vitro and in vivo studies (Mohammed et al. 2015; Nathan and Bellosta 1994; Nathan et al. 2002). These results suggest that the *APOE* ε4 allele may influence normal development and thus may block the putative stimulating educational effects on neuronal growth (Filippini et al. 2011; Mahley et al. 1995). These hypotheses are supported by reports showing that education has a protective effect on aging or brain pathological changes without observable deficits in cognition (Roe et al. 2007; Yasuno et al. 2015). On the other hand, according to the protective theory, the *APOE* ε4 allele disrupts educational protection. Education or cognitive reserve is known to protect against aging and pathological changes during cognitive decline, brain atrophy, and dysfunction in brain networks (Arenaza-Urquijo et al. 2013; Cheng 2016; Marques et al. 2016; Mungas et al. 2018; Yasuno et al. 2015). *APOE* ε4 carriers have been reported to have a less optimal topological organization of brain networks in both MCI and AD (Mohammed et al. 2015; Serra et al. 2017; Yao et al. 2015). Thus, the topological organization of functional brain networks influenced by education could be maintained even at an older age; however, this effect is likely reduced by the *APOE* ε4 allele. Finally, these findings regarding the topological properties suggest that the protective effects of education could be modified by the pathogenic mechanisms underlying the *APOE* allele.

Effects of interaction between genotype and education on nodal degree

Consistent with the global properties, significant associations between nodal degree and years of education were observed only in the *APOE* ε4 noncarriers but not in the carriers. The subjects with higher education exhibited a lower nodal degree in the temporal pole and inferior frontal gyrus (Fig. 3). Previous studies have demonstrated that these education-associated regions belong to the default mode network (DMN), including the left AMYG, the bilateral PHG, the right TPOsup and the bilateral TPOmid (Huang et al. 2016; J. Wang et al. 2015). A recent review also suggested that the cognitive reserve was associated with the DMN (Huang et al. 2016). For example, the studies reported that the connectivity between the dorsal attention network and DMN was associated with a weaker memory and differed between the MCI and normal aging groups (Franzmeier et al. 2017). Moreover, the regions in the medial temporal lobe are mainly involved in memory, including the functions of encoding and retrieval (Jackson and Schacter 2004; Spaniol et al. 2009), while the left inferior frontal gyrus is mainly associated with attention, which might regulate the memory function (Lundstrom et al. 2005; Spaniol et al. 2009). The nodal efficiency of the PHG.R in the white matter network mediates the effect of *APOE* ε4 on memory function (de Chastelaine et al. 2011). Higher education was found to be associated with lower FDG-PET metabolism in the temporo-parietal and ventral prefrontal brain areas (Ewers et al. 2013). These results may suggest that education can affect the functional connectivity and network properties of the brain regardless of the function of memory.

In addition, we demonstrated a positive association between the years of education and the nodal degree in the bilateral cuneus, which plays a role in visual information processing (Holmes et al. 2005; Vanni et al. 2001). Higher education leads to high-efficiency processing of visual information. In a previous study, the cognitive reserve exhibited a positive relationship with the left cuneus in the elderly compared with that in young subjects (Scarmeas et al. 2003). In another study, Tucker et al. also found a positive association between cognitive reserve and the right cuneus (Tucker and Stern 2011). This finding suggests that the protective effects of education are mainly present in the cuneus areas.

The *APOE* ε4 carriers and noncarriers showed considerably different associations with respect to education in the occipital and temporal lobes. We hypothesize that the difference observed in the associations might be due to the different patterns of brain damage between *APOE* ε4 noncarriers and carriers (den Heijer et al. 2002; Manning et al. 2014; Wolk and Mahley 2010). The noncarriers showed more frontoparietal atrophy (Wolk and Mahley 2010). In contrast, the *APOE* ε4 carriers exhibited greater hypometabolism and atrophy in the occipital and temporal lobes, especially the medial temporal lobe (MTL, including the hippocampus and PHG) and temporal pole (Agosta et al. 2009; den Heijer et al. 2002; Kim et al. 2015; Manning et al. 2014; Wolk and Mahley 2010). Moreover, through high-resolution structural imaging and diffusion tensor imaging techniques, one study showed that compared to noncarriers, ε4 carriers had a greater decrease in the parahippocampal white matter volume, suggesting that *APOE* ε4 might influence parahippocampal white matter changes (Honea et al. 2009). These regions mainly coincide with education-associated regions observed in *APOE* ε4 noncarriers but not in *APOE* ε4 carriers. Previous studies have reported that *APOE* ε4 carriers have greater Aβ deposition (Farlow et al. 2004; Honea et al. 2009; Jack et al. 2015; Liu et al. 2013) that may cause more severe brain atrophy (den Heijer et al. 2002) and increase the risk of cognitive impairment and dementia (Jack et al. 2015). These results indicate that the educational effects prevailing in these regions are reduced by Aβ deposition in individuals with *APOE* ε4 (Arenaza-Urquijo et al. 2017; Jack et al. 2015; Yasuno et al. 2015).

Limitations

Although the present study demonstrated that the significant correlations between education and the functional network properties persist only in *APOE* ε4 noncarriers, there are some limitations in this study. First, this study evaluated a small

number of subjects, especially in the normal aging and AD groups. In the ADNI2 database, only 110 subjects with initial or first screening visits had both fMRI and education information. Due to these limitations, determining the educational differences among the normal aging, MCI and AD groups in *APOE* carriers and noncarriers is challenging. Given that the data of ADNI subjects are continuously updated, future work is encouraged to assess a larger sample size and verify our current findings. Second, the range of the number of years of education was between 10 and 20. Thus, our study mainly included subjects who had attained a high-level education. As discussed above, the number of years of education might have a demographic influence on functional network and cognition. In individuals with low-level and high-level education attainment, the differences in the educational effects on the functional network with respect to the *APOE* genotype need to be further investigated.

Conclusions

In summary, we investigated the effects of education on functional brain networks among normal aging, MCI and AD groups in both *APOE* ε4 noncarriers and carriers using a graph theoretical analysis and resting-state fMRI. Our results indicated that the effects of education on the global and nodal properties of functional brain networks were mainly observed in the ε4 noncarriers but not in the ε4 carriers. The associations were mainly observed in normal aging and were reduced in MCI and AD. Our findings demonstrate that the protective effects of education persist in *APOE* ε4 noncarriers but were attenuated or reduced in ε4 carriers and diminished by the progression of AD.

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Compliance and ethical standards

Conflict of interest and disclosure The author(s) declared no conflicts of interest regarding the submission of this manuscript, and all of the authors have approved the manuscript for publication.

Human or animal subjects I verify that appropriate Institutional Review Board (IRB), Institutional Animal Care and Use Committee (IACUC), and/or ethics committee approval has been obtained for the use of human or animal subjects.

Ethical approval The data of ADNI2 are used in this study. The study subjects provided written informed consent at the time of enrollment for imaging and completed questionnaires approved by the institutional review board (IRB) of each participating site, including Good Clinical Practice guidelines, US 21CFR Part 50 – Protection of Human Subjects, and Part 56 – Institutional Review Boards (IRBs) / Research Ethics Boards (REBs), and pursuant to state and federal HIPAA regulations. Phone consents will be obtained for all pre-screening procedures and written informed consent for the study must be obtained from all participants and/or authorized representatives and the study partners before in person assessments are carried out.

Informed consent and HIPAA compliance Informed consent was obtained in accordance with US 21 CFR 50.25, the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada and ICH Good Clinical Practice. Applicable HIPAA privacy notifications were implemented and HIPAA authorizations signed before protocol procedures were carried out. Information was given in both oral and written form as deemed appropriate by the Site's IRB.

References

Agosta, F., Vossel, K. A., Miller, B. L., Migliaccio, R., Bonasera, S. J., Filippi, M., Gornotempini, M. L., et al. (2009). Apolipoprotein E epsilon4 is associated with disease-specific effects on brain atrophy in Alzheimer's disease and frontotemporal dementia. *Proceedings of the National Academy of Sciences of the United States of America, 106*(6), 2018–2022.

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., Phelps, C. H., et al. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers & Dementia, 7*(3), 270–279. https://doi.org/10.1016/j.jalz.2011.03.008.

Amieva, H., Mokri, H., Le Goff, M., Meillon, C., Jacqmin-Gadda, H., Foubert-Samier, A., Dartigues, J.-F., et al. (2014). Compensatory

mechanisms in higher-educated subjects with Alzheimer's disease: A study of 20 years of cognitive decline. *Brain, 137*(4), 1167–1175. https://doi.org/10.1093/brain/awu035.

Arenaza-Urquijo, E. M., Landeau, B., La Joie, R., Mevel, K., Mézenge, F., Perrotin, A., Chételat, G., et al. (2013). Relationships between years of education and gray matter volume, metabolism and functional connectivity in healthy elders. *NeuroImage, 83*, 450–457. https://doi.org/10.1016/j.neuroimage.2013.06.053.

Arenaza-Urquijo, E. M., Bejanin, A., Gonneaud, J., Wirth, M., La Joie, R., Mutlu, J., Chételat, G., et al. (2017). Association between educational attainment and amyloid deposition across the spectrum from normal cognition to dementia: Neuroimaging evidence for protection and compensation. *Neurobiology of Aging, 59*, 72–79. https://doi.org/10.1016/j.neurobiolaging.2017.06.016.

Barulli, D., & Stern, Y. (2013). Efficiency, capacity, compensation, maintenance, plasticity: Emerging concepts in cognitive reserve. *Trends in Cognitive Sciences, 17*(10), 502–509. https://doi.org/10.1016/j.tics.2013.08.012.

Bullmore, E., & Sporns, O. (2009). Complex brain networks: Graph theoretical analysis of structural and functional systems. *Nature Reviews Neuroscience, 10*(3), 186–198.

Cheng, S.-T. (2016). Cognitive reserve and the prevention of dementia: The role of physical and cognitive activities. *Current Psychiatry Reports, 18*(9), 85. https://doi.org/10.1007/s11920-016-0721-2.

Chiesa, P. A., Cavedo, E., Vergallo, A., Lista, S., Potier, M.-C., Habert, M.-O., Younesi, E., et al. (2019). Differential default mode network trajectories in asymptomatic individuals at risk for Alzheimer's disease. *Alzheimer's & Dementia, 15*(7), 940–950. https://doi.org/10.1016/j.jalz.2019.03.006.

de Chastelaine, M., Wang, T. H., Minton, B., Muftuler, L. T., & Rugg, M. D. (2011). The effects of age, memory performance, and callosal integrity on the neural correlates of successful associative encoding. *Cerebral Cortex, 21*(9), 2166–2176. https://doi.org/10.1093/cercor/bhq294.

Deco, G., Tononi, G., Boly, M., & Kringelbach, M. L. (2015). Rethinking segregation and integration: Contributions of whole-brain modelling. *Nature Reviews. Neuroscience, 16*(7), 430–439. https://doi.org/10.1038/nrn3963.

den Heijer, T., Oudkerk, M., Launer, L. J., van Duijn, C. M., Hofman, A., & Breteler, M. M. (2002). Hippocampal, amygdalar, and global brain atrophy in different apolipoprotein E genotypes. *Neurology, 59*(5), 746–748. https://doi.org/10.1212/wnl.59.5.746.

Ewers, M., Insel, P. S., Stern, Y., Weiner, M. W., & Alzheimer's Disease Neuroimaging, I. (2013). Cognitive reserve associated with FDG-PET in preclinical Alzheimer disease. *Neurology, 80*(13), 1194–1201. https://doi.org/10.1212/wnl.0b013e31828970c2.

Farlow, M. R., He, Y., Tekin, S., Xu, J., Lane, R., & Charles, H. C. (2004). Impact of APOE in mild cognitive impairment. *Neurology, 63*(10), 1898–1901.

Farrer, L. A., Cupples, L. A., Haines, J. L., Hyman, B., Kukull, W. A., Mayeux, R., Van Duijn, C. M., et al. (1997). Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease: A meta-analysis. *Jama, 278*(16), 1349–1356.

Filippini, N., Ebmeier, K. P., MacIntosh, B. J., Trachtenberg, A. J., Frisoni, G. B., Wilcock, G. K., Mackay, C. E., et al. (2011). Differential effects of the APOE genotype on brain function across the lifespan. *NeuroImage, 54*(1), 602–610. https://doi.org/10.1016/j.neuroimage.2010.08.009.

Franzmeier, N., Buerger, K., Teipel, S., Stern, Y., Dichgans, M., Ewers, M., & Alzheimer's Disease Neuroimaging, I. (2017). Cognitive reserve moderates the association between functional network anticorrelations and memory in MCI. *Neurobiology of Aging, 50*, 152–162. https://doi.org/10.1016/j.neurobiolaging.2016.11.013.

Franzmeier, N., Hartmann, J., Taylor, A. N. W., Araque-Caballero, M. A., Simon-Vermot, L., Kambeitz-Ilankovic, L., Ewers, M., et al. (2018). The left frontal cortex supports reserve in aging by enhancing functional network efficiency. *Alzheimer's Research & Therapy, 10*(1), 28. https://doi.org/10.1186/s13195-018-0358-y.

Holmes, A., Winston, J. S., & Eimer, M. (2005). The role of spatial frequency information for ERP components sensitive to faces and emotional facial expression. *Cognitive Brain Research, 25*(2), 508–520. https://doi.org/10.1016/j.cogbrainres.2005.08.003.

Honea, R. A., Vidoni, E., Harsha, A., & Burns, J. M. (2009). Impact of APOE on the healthy aging brain: A voxel-based MRI and DTI study. *Journal of Alzheimer's disease : JAD, 18*(3), 553–564. https://doi.org/10.3233/jad-2009-1163.

Huang, P., Fang, R., Li, B. Y., & Chen, S. D. (2016). Exercise-related changes of networks in aging and mild cognitive impairment brain. *Frontiers in Aging Neuroscience, 8*, 47. https://doi.org/10.3389/fnagi.2016.00047.

Jack, C. R., Wiste, H. J., Weigand, S. D., Knopman, D. S., Vemuri, P., Mielke, M. M., Machulda, M. M., et al. (2015). Age, sex, and APOE ε4 effects on memory, brain structure, and β-amyloid across the adult life span. *JAMA Neurology, 72*(5), 511–519.

Jackson, O., & Schacter, D. L. (2004). Encoding activity in anterior medial temporal lobe supports subsequent associative recognition. *NeuroImage, 21*(1), 456–462. https://doi.org/10.1016/j.neuroimage.2003.09.050.

Joo, W.-t., Kwak, S., Youm, Y., & Chey, J. (2017). Brain functional connectivity difference in the complete network of an entire village: The role of social network size and embeddedness. *Scientific Reports, 7*(1), 4465. https://doi.org/10.1038/s41598-017-04904-1.

Karch, C. M., & Goate, A. M. (2015). Alzheimer's Disease risk genes and mechanisms of Disease pathogenesis. *Biological Psychiatry, 77*(1), 43–51. https://doi.org/10.1016/j.biopsych.2014.05.006.

Kim, J. P., Seo, S. W., Shin, H. Y., Ye, B. S., Yang, J. J., Kim, C., Cho, H., et al. (2015). Effects of education on aging-related cortical thinning among cognitively normal individuals. *Neurology, 85*(9), 806–812.

Lenehan, M. E., Summers, M. J., Saunders, N. L., Summers, J. J., & Vickers, J. C. (2015). Relationship between education and age-related cognitive decline: A review of recent research. *Psychogeriatrics, 15*(2), 154–162. https://doi.org/10.1111/psyg.12083.

Liu, Y., Julkunen, V., Paajanen, T., Westman, E., Wahlund, L. O., Aitken, A., AddNeuroMed, C., et al. (2012). Education increases reserve against Alzheimer's disease–evidence from structural MRI analysis. *Neuroradiology, 54*(9), 929–938. https://doi.org/10.1007/s00234-012-1005-0.

Liu, C.-C., Kanekiyo, T., Xu, H., & Bu, G. (2013). Apolipoprotein E and Alzheimer disease: Risk, mechanisms and therapy. *Nature Reviews Neurology, 9*, 106–118. https://doi.org/10.1038/nrneurol.2012.263.

López, M. E., Turrero, A., Delgado, M. L., Rodríguezrojo, I. C., Arrazola, J., Barabash, A., Fernández, A., et al. (2018). APOE ε4 genotype and cognitive reserve effects on the cognitive functioning of healthy elders. *Dementia and Geriatric Cognitive Disorders, 44*(5–6), 328–342.

Lundstrom, B. N., Ingvar, M., & Petersson, K. M. (2005). The role of precuneus and left inferior frontal cortex during source memory episodic retrieval. *NeuroImage, 27*(4), 824–834. https://doi.org/10.1016/j.neuroimage.2005.05.008.

Lyketsos, C. G., Chen, L. S., & Anthony, J. C. (1999). Cognitive decline in adulthood: An 11.5-year follow-up of the Baltimore epidemiologic catchment area study. *The American Journal of Psychiatry, 156*(1), 58–65. https://doi.org/10.1176/ajp.156.1.58.

Mahley, R. W., Nathan, B. P., Bellosta, S., & Pitas, R. E. (1995). Apolipoprotein E: Impact of cytoskeletal stability in neurons and the relationship to Alzheimer's disease. *Current Opinion in Lipidology, 6*(2), 86–91.

Manning, E. N., Barnes, J., Cash, D. M., Bartlett, J. W., Leung, K. K., Ourselin, S., Alzheimer's Disease NeuroImaging, I, et al. (2014). APOE epsilon4 is associated with disproportionate progressive

hippocampal atrophy in AD. *PLoS One, 9*(5), e97608. https://doi.org/10.1371/journal.pone.0097608.

Marques, P., Soares, J. M., Magalhaes, R., Santos, N. C., & Sousa, N. (2015). The bounds of education in the human brain Connectome. *Scientific Reports, 5*, 12812. https://doi.org/10.1038/srep12812.

Marques, P., Moreira, P., Magalhães, R., Costa, P., Santos, N., Zihl, J., Sousa, N., et al. (2016). The functional connectome of cognitive reserve. *Hum Brain Mapp, 37*(9), 3310–3322. https://doi.org/10.1002/hbm.23242.

Martinez, J. H., Lopez, M. E., Ariza, P., Chavez, M., Pineda-Pardo, J. A., Lopez-Sanz, D., Buldu, J. M., et al. (2018). Functional brain networks reveal the existence of cognitive reserve and the interplay between network topology and dynamics. *Scientific Reports, 8*(1), 10525. https://doi.org/10.1038/s41598-018-28747-6.

Masters, C. L., Bateman, R., Blennow, K., Rowe, C. C., Sperling, R. A., & Cummings, J. L. (2015). Alzheimer's disease. *Nature Reviews Disease Primers, 1*, 18. https://doi.org/10.1038/nrdp.2015.56.

Mohammed, G., Ranjan, D., David, A. L., Qi, Z., Warren, B., Malek, A., & the Alzheimer's Disease Neuroimaging, I. (2015). Apolipoprotein-E4 (ApoE4) carriers show altered small-world properties in the default mode network of the brain. *Biomedical Physics & Engineering Express, 1*(1), 015001.

Mungas, D., Gavett, B., Fletcher, E., Farias, S. T., DeCarli, C., & Reed, B. (2018). Education amplifies brain atrophy effect on cognitive decline: Implications for cognitive reserve. *Neurobiology of Aging, 68*, 142–150. https://doi.org/10.1016/j.neurobiolaging.2018.04.002.

Nathan, B. P., & Bellosta, S. (1994). Differential effects of apolipoproteins E3 and E4 on neuronal growth in vitro. *Science, 264*(5160), 850–852.

Nathan, B. P., Jiang, Y., Wong, G. K., Shen, F., Brewer, G. J., & Struble, R. G. (2002). Apolipoprotein E4 inhibits, and apolipoprotein E3 promotes neurite outgrowth in cultured adult mouse cortical neurons through the low-density lipoprotein receptor-related protein. *Brain Research, 928*(1–2), 96–105.

Perry, A., Wen, W., Kochan, N. A., Thalamuthu, A., Sachdev, P. S., & Breakspear, M. (2017). The independent influences of age and education on functional brain networks and cognition in healthy older adults. *Hum Brain Mapp, 38*(10), 5094–5114. https://doi.org/10.1002/hbm.23717.

Posner, M. I., & Rothbart, M. K. (2005). Influencing brain networks: Implications for education. *Trends in Cognitive Sciences, 9*(3), 99–103. https://doi.org/10.1016/j.tics.2005.01.007.

Reitz, C., & Mayeux, R. (2014). Alzheimer disease: Epidemiology, diagnostic criteria, risk factors and biomarkers. *Biochemical Pharmacology, 88*(4), 640–651. https://doi.org/10.1016/j.bcp.2013.12.024.

Roe, C. M., Xiong, C., Miller, J. P., & Morris, J. C. (2007). Education and Alzheimer disease without dementia: Support for the cognitive reserve hypothesis. *Neurology, 68*(3), 223–228. https://doi.org/10.1212/01.wnl.0000251303.50459.8a.

Scarmeas, N., Zarahn, E., Anderson, K. E., Hilton, J., Flynn, J., Van Heertum, R. L., Stern, Y., et al. (2003). Cognitive reserve modulates functional brain responses during memory tasks: A PET study in healthy young and elderly subjects. *NeuroImage, 19*(3), 1215–1227. https://doi.org/10.1016/s1053-8119(03)00074-0.

Seeman, T. E., Huang, M. H., Bretsky, P., Crimmins, E., Launer, L., & Guralnik, J. M. (2005). Education and APOE-e4 in longitudinal cognitive decline: MacArthur studies of successful aging. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences, 60*(2), P74.

Selkoe, D. J. (2005). Defining molecular targets to prevent Alzheimer disease. *Archives of Neurology, 62*(2), 192–195. https://doi.org/10.1001/archneur.62.2.192.

Serra, L., Cercignani, M., Petrosini, L., Basile, B., Perri, R., Fadda, L., Bozzali, M., et al. (2011). Neuroanatomical correlates of cognitive reserve in Alzheimer disease. *Rejuvenation Research, 14*(2), 143–151. https://doi.org/10.1089/rej.2010.1103.

Serra, L., Mancini, M., Cercignani, M., Di Domenico, C., Spano, B., Giulietti, G., Bozzali, M., et al. (2017). Network-based substrate of cognitive Reserve in Alzheimer's Disease. *Journal of Alzheimer's disease : JAD, 55*(1), 421–430. https://doi.org/10.3233/JAD-160735.

Spaniol, J., Davidson, P. S. R., Kim, A. S. N., Han, H., Moscovitch, M., & Grady, C. L. (2009). Event-related fMRI studies of episodic encoding and retrieval: Meta-analyses using activation likelihood estimation. *Neuropsychologia, 47*(8–9), 1765–1779. https://doi.org/10.1016/j.neuropsychologia.2009.02.028.

Sporns, O. (2011). The human connectome: A complex network. *Annals of the New York Academy of Sciences, 1224*, 109–125. https://doi.org/10.1111/j.1749-6632.2010.05888.x.

Stern, Y. (2006). Cognitive reserve and Alzheimer disease. *Alzheimer Disease & Associated Disorders, 20*(3), S69–S74. https://doi.org/10.1097/00002093-200607001-00010.

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia, 47*(10), 2015–2028. https://doi.org/10.1016/j.neuropsychologia.2009.03.004.

Stern, Y. (2012). Cognitive reserve in ageing and Alzheimer's disease. *The Lancet Neurology, 11*(11), 1006–1012. https://doi.org/10.1016/s1474-4422(12)70191-6.

Tucker, A. M., & Stern, Y. (2011). Cognitive reserve in aging. *Current Alzheimer Research, 8*(4), 354–360. https://doi.org/10.2174/156720511795745320.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Joliot, M., Mazoyer, B., et al. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage, 15*(1), 273–289.

Vanni, S., Tanskanen, T., Seppä, M., Uutela, K., & Hari, R. (2001). Coinciding early activation of the human primary visual cortex and anteromedial cuneus. *Proceedings of the National Academy of Sciences of the United States of America, 98*(5), 2776–2780. https://doi.org/10.1073/pnas.041600898.

Vecchio, F., Miraglia, F., Marra, C., Quaranta, D., Vita, M. G., Bramanti, P., & Rossini, P. M. (2014). Human brain networks in cognitive decline: A graph theoretical analysis of cortical connectivity from EEG data. *Journal of Alzheimer's disease : JAD, 41*(1), 113–127. https://doi.org/10.3233/jad-132087.

Wang, J., Wang, X., He, Y., Yu, X., Wang, H., & He, Y. (2015). Apolipoprotein E epsilon4 modulates functional brain connectome in Alzheimer's disease. *Human Brain Mapping, 36*(5), 1828–1846. https://doi.org/10.1002/hbm.22740.

Wang, X. N., Zeng, Y., Chen, G. Q., Zhang, Y. H., Li, X. Y., Hao, X. Y., Li, Y. X., et al. (2016). Abnormal organization of white matter networks in patients with subjective cognitive decline and mild cognitive impairment. *Oncotarget, 7*(31), 48953–48962.

Watts, D. J., & Strogatz, S. H. (1998). Collective dynamics of 'small-world' networks. *Nature, 393*(6684), 440–442. https://doi.org/10.1038/30918.

Winnock, M., Letenneur, L., Jacqmingadda, H., Dallongeville, J., Amouyel, P., & Dartigues, J. F. (2002). Longitudinal analysis of the effect of apolipoprotein E ε4 and education on cognitive performance in elderly subjects: The PAQUID study. *Journal of Neurology, Neurosurgery, and Psychiatry, 21*(6), 794–797.

Wolk, D. A., & Mahley, R. W. (2010). Apolipoprotein E (APOE) genotype has dissociable effects on memory and attentional-executive network function in Alzheimer's disease. *Proceedings of the National Academy of Sciences of the United States of America, 107*(22), 10256–10261.

Xia, M. R., Wang, J. H., & He, Y. (2013). BrainNet viewer: A network visualization tool for human brain Connectomics. *PLoS One, 8*(7), 15. https://doi.org/10.1371/journal.pone.0068910.

Xu, W., Tan, L., Wang, H. F., Tan, M. S., Tan, L., Li, J. Q., Yu, J. T., Zhao, Q. F., et al. (2016). Education and risk of dementia: Dose-response meta-analysis of prospective cohort studies. *Molecular Neurobiology, 53*(5), 3113–3123. https://doi.org/10.1007/s12035-015-9211-5.

Yan, T. Y., Wang, Y. H., Weng, Z. Z., Du, W. Y., Liu, T. T., Chen, D. D., Han, Y., et al. (2019). Early-stage identification and pathological development of Alzheimer's Disease using multimodal MRI. *Journal of Alzheimers Disease, 68*(3), 1013–1027. https://doi.org/10.3233/jad-181049.

Yao, Z., Hu, B., Zheng, J., Zheng, W., Chen, X., Gao, X., Alzheimer's Disease Neuroimaging, I, et al. (2015). A FDG-PET study of metabolic networks in Apolipoprotein E ε4 allele carriers. *PLoS One, 10*(7), e0132300. https://doi.org/10.1371/journal.pone.0132300.

Yasuno, F., Kazui, H., Morita, N., Kajimoto, K., Ihara, M., Taguchi, A., Kishimoto, T., et al. (2015). Low amyloid-β deposition correlates with high education in cognitively normal older adults: A pilot study. *International Journal of Geriatric Psychiatry, 30*(9), 919–926. https://doi.org/10.1002/gps.4235.

Zahodne, L. B., Stern, Y., & Manly, J. J. (2015). Differing effects of education on cognitive decline in diverse elders with low versus high educational attainment. *Neuropsychology, 29*(4), 649–657. https://doi.org/10.1037/neu0000141.

Zhao, X., Liu, Y., Wang, X., Liu, B., Xi, Q., Guo, Q., Wang, P., et al. (2012). Disrupted small-world brain networks in moderate Alzheimer's Disease: A resting-state fMRI study. *PLoS One, 7*(3), e33540. https://doi.org/10.1371/journal.pone.0033540.