

# Effect of APOE $\epsilon$ 4 on Functional Brain Network in Patients with Subjective Cognitive Decline: A Resting State Functional MRI Study

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**Purpose:** Subjective cognitive decline (SCD) is the earliest symptom stage of Alzheimer's disease (AD), and the APOE $\epsilon$ 4 allele is the strongest genetic risk factor for sporadic AD. Based on graph theory, the resting state functional connectivity (rsFC) in SCD patients with APOE $\epsilon$ 4 was studied to explore the effect of APOE $\epsilon$ 4 on the rsFC network properties of SCD patients.

**Patients and Methods:** This cross-sectional study included MRI image data from 19 SCD patients with APOE $\epsilon$ 4 (SCD+), 29 SCD patients without APOE $\epsilon$ 4 (SCD-), and 30 normal control (NC-) individuals without APOE $\epsilon$ 4. We generated a binary matrix based on anatomical automatic labeling (AAL) 90 atlas to construct the functional network. We then calculated the whole brain network characteristics and intracerebral node characteristics by graph theory.

**Results:** For the whole brain network characteristics, all three groups showed small-worldness. The SCD+ group had increased compensatory information transfer speed and enhanced integration capability. This group also had high heterogeneity for intracerebral node characteristics, mainly in the default mode network, left superior occipital gyrus, and bilateral putamen.

**Conclusion:** APOE $\epsilon$ 4 effects the functional brain network in patients with SCD and may be a potential indicator for the identification of SCD.

**Keywords:** SCD, APOE $\epsilon$ 4 allele, graph theory, whole brain network characteristics, intracerebral node characteristics

## Introduction

The incidence of dementia has markedly increased with the aging of the population.<sup>1</sup> Alzheimer's disease (AD) is the most common cause for senile dementia, and nearly 50 million patients worldwide were reported to have AD dementia in 2018 (a statistic that is expected to triple in the next 25 years).<sup>1</sup> As a progressive and irreversible neurodegenerative disease,<sup>2</sup> AD presents vast societal and familial burdens that would be somewhat alleviated with additional knowledge about the pathophysiology of the disease. To understand the mechanism of AD and its treatment, research at the preclinical level is crucial.<sup>1,3</sup> Subjective cognitive decline (SCD) is the preclinical period of AD and the earliest symptom stage. In this state, patients may subjectively experience a cognitive decline, although neuropsychiatric assessment often appears normal.<sup>4</sup> The progression of SCD to mild cognitive impairment (MCI; 27%) and AD (14%) is relatively rare,<sup>5</sup> and most SCD

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patients will not experience progressive cognitive decline.<sup>4</sup> Because self-perception and neuropsychological methods of diagnosis are often unreliable, we explored whether risk factors appear in early SCD that promote disease progression. Indeed, AD risk factors impact disease progression, but whether AD risk factors can be used as potential indicators to predict SCD progression remains unclear. Here, we explored the influence of AD risk factors on SCD patients.

The Apolipoprotein E4 (APOE $\epsilon$ 4) allele is the strongest known genetic risk factor for sporadic AD.<sup>6</sup> Risk of developing AD in carriers of the APOE $\epsilon$ 4 (individuals with at least one APOE $\epsilon$ 4 allele, genotypes  $\epsilon$ 4/ $\epsilon$ 4,  $\epsilon$ 4/ $\epsilon$ 3) monoallele is 3- to 4-fold higher than general population; the possibility of carriers of the diallele developing AD is 9- to 15-fold higher.<sup>7-10</sup> Furthermore, the possibility of carriers developing MCI is 2.2- to 6.2-fold higher than that of non-carriers of APOE $\epsilon$ 4.<sup>11</sup> Finally, the risk for progression to AD in APOE $\epsilon$ 4 carriers with previously existing cognitive disorders or MCI is 4.1- to 25-fold higher than in non-carriers.<sup>12</sup> To confirm whether carrying APOE $\epsilon$ 4 is a risk factor for SCD progression, we used graph theory analysis of resting-state functional magnetic resonance imaging (rs-fMRI) to observe the characteristics of brain network organization, clarify the internal activities of the brain, and describe and predict dysfunction from the perspective of the network.<sup>13</sup>

In elderly carriers of the APOE $\epsilon$ 4 allele, resting state functional connectivity (rsFC) changes before A $\beta$  deposition.<sup>14</sup> Default mode network (DMN) functional connectivity (FC) changes in rsFC connectivity also occur in the frontal and posterior lobes, as well as in the right hippocampus in the DMN of SCD patients, although frontal lobe FC in carriers of the APOE $\epsilon$ 4 allele increases relatively slowly.<sup>15</sup> Importantly, FC can be used as one of the earliest potential neuroimaging markers for neurodegenerative disease.<sup>16</sup>

Here, we hypothesized that (1) APOE $\epsilon$ 4 effects the functional brain network in patients with SCD, and (2) APOE $\epsilon$ 4 may be used as an indicator to identify the progress of SCD. To test these hypotheses, we obtained rs-fMRI data from 34 normal control individuals without APOE $\epsilon$ 4 (NC-), 20 SCD patients with at least one APOE $\epsilon$ 4 allele (SCD+), and 34 SCD patients without APOE $\epsilon$ 4 (SCD-) from the Alzheimer's Disease Neuroimaging Initiative (ADNI). We then constructed a functional brain network based on graph theory and analyzed relevant rsFC data.

## Patients and Methods

### Study Subjects

All raw data used in this study, including neuropsychological assessment scale, MRI images, and biomarker data of cerebrospinal fluid (CSF), were obtained from the ADNI (adni.loni.usc.edu) project. As a longitudinal, multicenter study designed to develop clinical, imaging, genetic, and biochemical biomarkers, the ADNI project strives to develop methods for the early detection and subsequent tracking of AD. According to ADNI standard operating procedures, the current study was approved by the Institutional Review Board (IRB) of all participating centers in ADNI. We obtained the approval of our local ethics review committee (Dongguan Tung Wah Hospital medical ethics committee 2019DHLL052) before analysis began. The study included 54 patients with SCD (baseline SCD patients with neuropsychological assessment, CSF biomarkers, APOE genotyping information and 3.0 rs-fMRI data in the ADNI2 database), and 54 normal controls (NC) in a 1:1 random ratio. NC and SCD patients were further divided into the APOE $\epsilon$ 4+ group and APOE $\epsilon$ 4- group based on whether they carried the APOE $\epsilon$ 4 gene. The 54 NC participants included 20 normal control individuals with APOE $\epsilon$ 4 (NC+) and 34 cases of NC-; the 54 patients with SCD included 20 cases of SCD+ and 34 SCD-. To avoid unwanted effects of APOE $\epsilon$ 4 on the results of the current study, the number of NC- patients was relatively small. The diagnostic criteria of SCD included: 1) self-reported patient memory loss (combined with a contradictory statement by a caregiver); 2) normal cognitive range on a delayed recall test of the Wechsler Memory Scale-Logical Memory (WMS-LM) task; 3) Mini-Mental State Examination (MMSE) evaluation; and 4) Clinical Dementia Rating Scale (CDR) evaluation. Inclusion criteria of the NC group: no memory impairment or decline as reported by both the patient and caregiver; and comparable scores to SCD patients on test of delayed recall of WMS-LM, MMSE, and CDR. Demographic data included age, sex, and educational level; neuropsychological tests included 1) MMSE; 2) delayed recall of WMS-LM; 3) Alzheimer's Disease Assessment Scale 13 (ADAS13); 4) Rey Auditory Verbal Learning Test (RAVLT) immediate; and 5) Trail Making Test Part B (TMT-B). Importantly, these tests have been previously associated with SCD progression.<sup>17</sup> Finally, CSF biomarkers included  $\beta$ -amyloid protein 1-42 (A $\beta$ <sub>1-42</sub>), total tau

(t-tau), and phosphorylated tau<sub>181</sub> (p-tau<sub>181</sub>); all analyzed subjects had CSF data.

## Collection and Preprocessing of MRI Data

All subjects were selected from ADNI2, and structural MRI and rs-fMRI data were obtained for each participant via a 3.0 MRI scanner. Structural MRI images were obtained according to the following scanning parameters: Acquisition Plane=SAGITTAL; Acquisition Type=3D; Coil=PA; Field Strength=3.0 tesla; Flip Angle=9.0 degree; Manufacturer=SIEMENS; Matrix X=240.0 pixels; Matrix Y=256.0 pixels; Matrix Z=176.0; Mfg Model=Prisma\_fit; Pixel Spacing X=1.1 mm; Pixel Spacing Y=1.1 mm; Pulse Sequence=GR/IR; Slice Thickness=1.2 mm; TE=3.0 ms; TI=900.0 ms; TR=2300.0 ms; and Weighting=T1. rs-fMRI images were obtained at the following scanning parameters: Field Strength=3.0 tesla; Flip Angle=90.0 degree; Manufacturer=SIEMENS; Matrix X=448.0 pixels; Matrix Y=448.0 pixels; Mfg Model=Prisma; Pixel Spacing X=3.4 mm; Pixel Spacing Y=3.4 mm; Pulse Sequence=EP; Slices=197.0; Slice Thickness=3.4 mm; TE=30.0 ms; and TR=3000.0 ms.

All rs-fMRI data were pre-processed<sup>13</sup> using the resting-state functional magnetic resonance imaging data processing toolkit Restplus 1.7 (<http://www.restfmri.net/forum/RESTplusV1.7>),<sup>18</sup> which is based on Statistical Parametric Mapping (SPM12, <https://www.fil.ion.ucl.ac.uk/spm/software/spm12>) on the MATLAB R2013b platform (The MathWorks Inc., Natick, MA, US) per manufacturer's recommendation. Briefly, we first converted the data format using dcm2nii to convert the functional image and structural image of the original data into nifti format files. We then removed the first 10 time points due to initial patient and machine instability. Finally, we corrected the time layer (one process for each scan: the interpolation method was used to assure accuracy in the results). The scanning order included the interlayer scan at the beginning of each odd layer; 4. Head motion correction by displacement and rotation threshold values of 3 mm and 3 degrees, respectively. If displacement of head motion exceeded 3 mm or the rotation angle exceeded 3 degrees, the subject was excluded; 5. Spatial standardization, using the echo planar imaging (EPI) registration method, spatial standardization, and data registration to the standard space; 6. De-linear trending due to potential linear drift; 7. Filtration using the effective frequency band

of 0.01–0.08 Hz; and 8. Regression covariate analysis (white matter, CSF, and cephalic noise).

## Construction and Analysis of Brain Network

The anatomical automatic labeling (AAL) 90 atlas<sup>19</sup> was used as the brain region template. Whole brain images were divided into 90 distinct regions, and each was considered a node in the brain network. Pearson's correlation coefficient between the time series of each pair of regions of interest was calculated using MATLAB-based GRETNA software (The Graph-theoretical Network Analysis Toolkit, [www.nitrc.org](http://www.nitrc.org))<sup>20</sup> to generate a binary matrix and construct the functional network.<sup>21</sup>

## Network Properties

To characterize the topological organization of the rsFC network, the following whole brain network characteristics were assessed: small-worldness, global efficiency, local efficiency, characteristic path length, clustering coefficient, and assortativity. For intracerebral node characteristics, we considered nodal efficiency, nodal local efficiency, degree centrality, and betweenness centrality. For the definitions of these network properties and their computations, refer to Rubinov et al,<sup>22</sup> as shown in [Supplementary File 1](#).

## Statistical Analysis

SPSS 20.0 statistical analysis software was used for the analysis of demographic data, neuropsychological assessment, and CSF biomarkers. For continuous variables, one-way analysis of variance (ANOVA) was used. Two sample *t*-test was then performed for significant results. For binary variables (such as sex), the  $\chi^2$  test was used.  $P < 0.05$  was considered statistically significant. The network properties were analyzed by one-way ANOVA F-test and two-sample *t*-test in the Global and Nodal Metric Comparison module of GRETNA for each of the three groups. An AAL90 template was used where the sparsity was 0.05–0.26, the interval was 0.01 (sparsity  $\leq 0.26$ , 90% of the subjects have small-world attributes), and the number of iterations was 500. For significant results, a two-sample *t*-test was used for post hoc analysis and the threshold was set to  $p < 0.05$ . Multiple comparison correction (few and *fdr*) was then performed. None passed the correction, and the uncorrected results were selected.

## Results

### Demographic Data

This study included 30 NC<sup>-</sup>, 29 SCD<sup>-</sup> and 19 SCD<sup>+</sup> subjects (nine participants were excluded due to poor image quality). Table 1 summarizes demographics, neuropsychological evaluation, and CSF biomarkers of each group. No significant differences were observed in sex, educational level, or neuropsychological performance between the three groups ( $p>0.05$ ). The SCD<sup>+</sup> group (69.82±5.18 years) was significantly younger than the SCD<sup>-</sup> group (72.17±4.91 years) ( $p=0.014$ ) and NC<sup>-</sup> group (74.50±5.86 years) ( $p=0.014$ ); had significantly higher TAU levels (281.87±100.14 pg/mL) than the SCD<sup>-</sup> group (207.53±74.37 pg/mL) ( $p=0.004$ ) and NC<sup>-</sup> group (225.49±64.00 pg/mL) ( $p=0.004$ ); and had significantly higher PTAU levels (26.41±11.19 pg/mL) than the SCD<sup>-</sup> group (18.31±6.92 pg/mL) ( $p=0.002$ ) and NC<sup>-</sup> group (19.12±5.87 pg/mL) ( $p=0.002$ ). Hence, these three indicators were used as regression covariates for statistical analysis in subsequent image processing; the significance threshold was set to  $p<0.05$ .

### Whole Brain Network Characteristics

When the sparsity value is 0.05–0.26 and the interval is 0.01, the area under the curve (AUC) acts as an independent variable for statistical comparison between

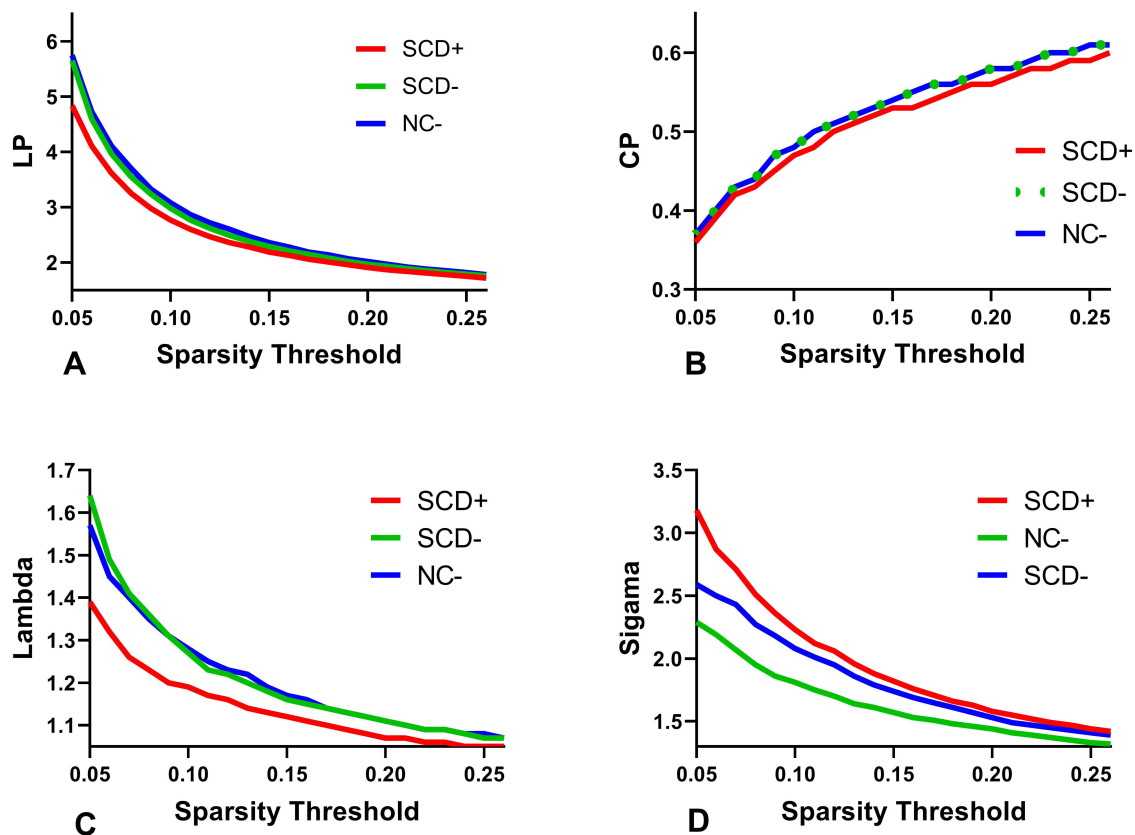
groups. Whole brain network characteristic results among SCD<sup>+</sup>, SCD<sup>-</sup>, and NC<sup>-</sup> patients are shown in Figures 1 and 2 and Table 2. SCD<sup>+</sup>, SCD<sup>-</sup>, and NC<sup>-</sup> groups all showed small-world property in the functional network, characterized by normalized clustering coefficients ( $\gamma$ ) ( $\gamma>1$ ) and normalized characteristic path length ( $\lambda$ ) ( $\lambda\approx 1$ ). SCD<sup>+</sup>, SCD<sup>-</sup>, and NC<sup>-</sup> groups were within the wider sparse threshold range (0.05~0.26). The AUC of shortest path length (LP) (0.5104±0.6413) (Figure 1A,  $p=0.035$ ) and  $\lambda$  (0.2387±0.0056) (Figures 1C and 2A,  $p=0.000$ ) was significantly lower in the SCD<sup>+</sup> group compared to the SCD<sup>-</sup> group (0.5431±0.6287, 0.2525±0.0142) and NC<sup>-</sup> group (0.5588±0.6113, 0.2531±0.0133); there was no significant change in clustering coefficient (CP). The small-world property ( $\sigma$ ) was defined by CP and LP,  $\sigma=\gamma/\lambda$ , and the  $\sigma$  value of SCD<sup>+</sup> group increased. The AUC of global efficiency was higher in the SCD<sup>+</sup> group (0.936±0.0752) compared to the NC<sup>-</sup> group (0.872±0.0749) (Figure 2B,  $p=0.023$ ), although the SCD<sup>+</sup> group had lower assortativity (0.490±0.1551) than the SCD<sup>-</sup> (0.638±0.1980) and NC<sup>-</sup> (0.601±0.1591) groups (Figure 2C,  $p=0.017$ ). Statistical analyses were performed with and without regression covariates, although no differences were observed.

**Table 1** Differences in Demographic Characteristics, Neuropsychological Assessment, and Cerebrospinal Fluid Biomarkers Among Three Groups of Subjects

	NC <sup>-</sup> (n=30)	SCD <sup>-</sup> (n=29)	SCD <sup>+</sup> (n=19)	F/ $\chi^2$	p
Age (years)	74.50±5.86	72.17±4.91	69.82±5.18	4.502 <sup>a</sup>	0.014*
Sex (F/M)	14/16	19/10	10/9	0.821 <sup>b</sup>	0.365
Education	16.46±2.46	16.17±2.82	17.05±2.72	0.684 <sup>a</sup>	0.508
ADAS13	8.94±4.16	8.72±4.22	8.15±3.73	0.219 <sup>a</sup>	0.804
MMSE	28.87±1.36	29.00±1.07	29.00±1.37	0.103 <sup>a</sup>	0.902
RAVLT	44.40±9.91	47.69±9.76	44.89±9.74	0.923 <sup>a</sup>	0.402
WMS-LM	13.83±2.23	12.69±3.16	14.11±3.83	1.596 <sup>a</sup>	0.210
TMT-B	79.97±39.20	78.97±30.62	83.42±32.21	0.099 <sup>a</sup>	0.906
ABETA (pg/mL)	1359.99±394.08	1342.30±393.44	1133.25±397.27	2.250 <sup>a</sup>	0.112
TAU (pg/mL)	225.49±64.00	207.53±74.37	281.87±100.14	5.941 <sup>a</sup>	0.004*
PTAU (pg/mL)	19.12±5.87	18.31±6.92	26.41±11.19	7.008 <sup>a</sup>	0.002*

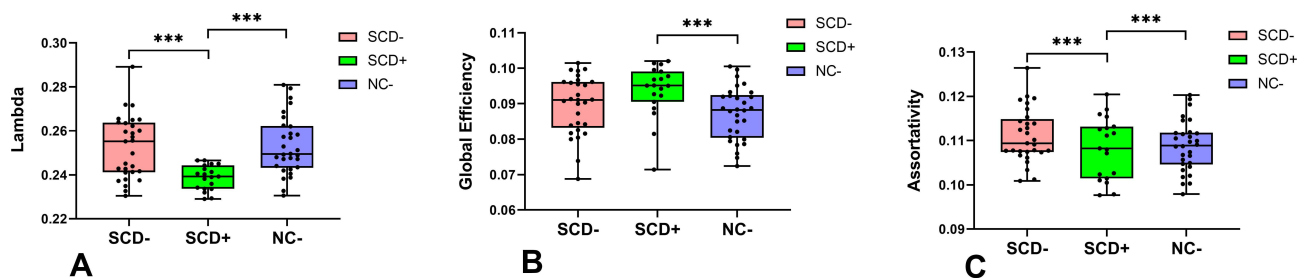
**Notes:** Data are presented as the mean±SD. \* $P<0.05$  indicates significant differences between the groups. <sup>a</sup>F value was obtained by using the analysis of variance test. <sup>b</sup> $\chi^2$  value was obtained using the chi-square test.

**Abbreviations:** SCD<sup>+</sup>, subjective cognitive decline with APOE $\epsilon$ 4; SCD<sup>-</sup>, subjective cognitive decline without APOE $\epsilon$ 4; NC<sup>-</sup>, normal control without APOE $\epsilon$ 4; F, female; M, male; ADAS13, Alzheimer's Disease Assessment Scale 13; MMSE, Mini Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test; WMS-LM, Wechsler Memory Scale Logical; TMT-B, Trail Making Test Part B.



**Figure 1** Small-world parameters of the global cerebral resting-state functional network among three groups of subjects at a sparsity rating of 0.05–0.26. **(A)** LP, Shortest path length, compared with that of the NC- and SCD-; the LP of the SCD+ was not significantly different ( $P>0.05$ ). **(B)** CP, Clustering coefficient, compared with that of the NC- and SCD-; the CP of the SCD+ was not significantly different ( $P>0.05$ ). **(C)** Lambda ( $\lambda$ ), Normalized characteristic path length, compared with that of the NC- and SCD-; the LP of the SCD+ was significantly decreased ( $P<0.05$ ). **(D)** Sigma ( $\sigma$ ), Small-worldness, compared with that of the NC- and SCD-; the  $\sigma$  of the SCD+ was not significantly different ( $P>0.05$ ).

**Abbreviations:** SCD+, subjective cognitive decline with APOE $\epsilon$ 4; SCD-, subjective cognitive decline without APOE $\epsilon$ 4; NC-, normal control without APOE $\epsilon$ 4; LP, shortest path length; CP, clustering coefficient;  $\lambda$ , normalized characteristic path length;  $\sigma$ , small-worldness.



**Figure 2** Characteristics of global properties among three groups of subjects with statistical significance. **(A)** Lambda ( $\lambda$ ), Normalized characteristic path length, compared with that of the NC- and SCD-; the  $\lambda$  of the SCD+ was significantly decreased ( $P<0.05$ ). **(B)** Global Efficiency, compared with that of the NC-; the global efficiency of the SCD+ was significantly increased ( $P<0.05$ ). **(C)** Assortativity, compared with that of the NC- and SCD-; the assortativity of the SCD+ was significantly increased ( $P<0.05$ ). \*\*\* indicates statistically significant.

**Abbreviations:** SCD+, subjective cognitive decline with APOE $\epsilon$ 4; SCD-, subjective cognitive decline without APOE $\epsilon$ 4; NC-, normal control without APOE $\epsilon$ 4.

## Intracerebral Node Characteristics

We then compared node characteristics in the functional network between the SCD+ group and SCD- and NC- groups. The SCD+ group had high heterogeneity in intracerebral node characteristics, particularly in the DMN, left superior occipital gyrus, and bilateral

putamen. The specific manifestations were as follows: lower local efficiency at the superior occipital gyrus node and higher local efficiency in three discrete regions including the right putamen, posterior cingulate cortex, and left putamen ( $p<0.05$ ; Figure 3, Table 3); In addition, the SCD+ group had higher degree centrality at the

**Table 2** Characteristics of Global Properties Among Three Groups of Subjects

Global Properties	SCD+	SCD-	NC-	F value	P value
CP	0.1083±0.0692	0.1110±0.0605	0.1087±0.0573	1.530	0.233
LP	0.5104±0.6413	0.5431±0.6287	0.5588±0.6113	3.502	0.035*
$\lambda$	0.2387±0.0056	0.2525±0.0142	0.2531±0.0133	9.452	0.000*
$\sigma$	0.4062±0.0814	0.3809±0.1019	0.3425±0.0945	2.844	0.064
Eg	0.936±0.0752	0.896±0.0823	0.872±0.0749	3.961	0.023*
Assortativity	0.490±0.1551	0.638±0.1980	0.601±0.1591	4.310	0.017*
Eloc	0.1402±0.0818	0.1403±0.0909	0.1367±0.0813	1.599	0.209

**Notes:** Data are presented as the mean±SD. \*P<0.05 indicates significant differences between the groups. F value was obtained by using the analysis of variance test.

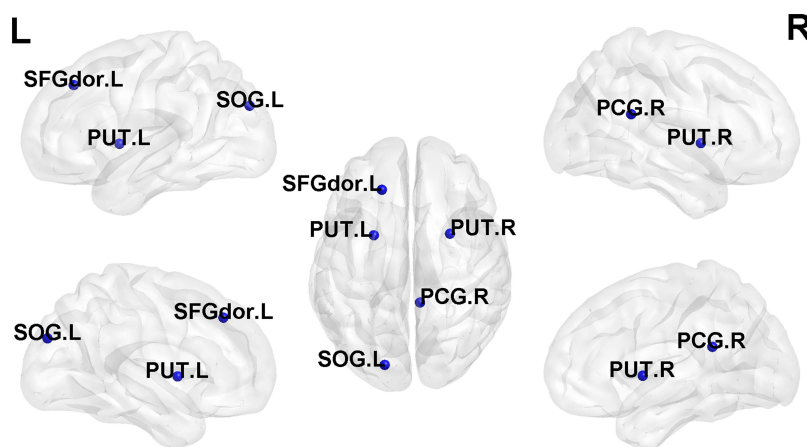
**Abbreviations:** SCD+, subjective cognitive decline with APOE $\epsilon$ 4; SCD-, subjective cognitive decline without APOE $\epsilon$ 4; NC-, normal control without APOE $\epsilon$ 4; CP, clustering coefficient; LP, shortest path length;  $\lambda$ , normalized characteristic path length;  $\sigma$ , small-worldness; Eg, global efficiency; Eloc, local efficiency.

posterior cingulate cortex, although lower degree centrality at the dorsolateral superior frontal gyrus ( $p<0.05$ ; Figure 3, Table 4). Statistical analyses were performed with and without regression covariates separately, which revealed no difference.

## Discussion

In seeking to understand the mechanism and treatment of AD, current research is heavily focused on the early stage of the disease.<sup>23</sup> Thus, patients with SCD ability are valuable individuals looking for preclinical AD.<sup>24</sup> This study investigated whether there are rsFC changes in SCD patients with the APOE $\epsilon$ 4 allele in terms of whole brain network characteristics and intracerebral node characteristics. The effect of APOE $\epsilon$ 4 on the functional brain network of SCD

patients was examined. We utilized graph theory-based analysis to determine whether the SCD+ group had similar rsFC changes to MCI and AD relative to the SCD- and NC- groups. In support of our hypotheses, the three groups each presented with small-world properties; however, the SCD+ group had significantly lower LP than the SCD- and NC- groups but higher global efficiency than the NC- group, with compensatory information transfer speed increase and enhanced integration capability. The SCD+ group rsFC was highly heterogeneous at intracerebral nodes but showed similar abnormal DMN region connectivity to MCI or AD (higher at the level of the posterior cingulate cortex and lower in the dorsolateral superior frontal gyrus), together with compensatory effects at the bilateral putamen and left superior occipital gyrus.



**Figure 3** Differences in nodal local efficiency and degree centrality (DC) among subjective cognitive decline with APOE $\epsilon$ 4 (SCD+), subjective cognitive decline without APOE $\epsilon$ 4 (SCD-) and normal control without APOE $\epsilon$ 4 (NC-). The statistical criterion for groups was set at  $P<0.05$ , uncorrected.

**Abbreviations:** SFGdor.L, superior frontal gyrus, dorsolateral, left; SOG.L, superior occipital gyrus, left; PUT.L, lenticular nucleus, putamen, left; PUT.R, lenticular nucleus, putamen, right; PCG.R, posterior cingulate gyrus, right.

**Table 3** Brain Regions with Significant Nodal Local Efficiency Differences Between the Groups

AAL Number	Corresponding Brain Regions	P	F
49	Occipital_Sup_L	0.0106	4.8584
74	Putamen_R	0.0181	4.2479
36	Cingulum_Post_R	0.0424	3.3085
73	Putamen_L	0.0447	3.2509

**Notes:** Data are presented as the mean±SD. P<0.05 indicates significant differences between the groups. F value was obtained by using the analysis of variance test.

**Abbreviation:** AAL, automated anatomical labeling.

**Table 4** Brain Regions with Significant Degree Centrality Differences Between Groups

AAL Number	Corresponding Brain Regions	P	F
36	Cingulum_Post_R	0.0057	5.5695
3	Frontal_Sup_L	0.0120	4.7147

**Notes:** Data are presented as the mean±SD. P<0.05 indicates significant differences between the groups. F value was obtained by using the analysis of variance test.

**Abbreviation:** AAL, automated anatomical labeling.

At the whole brain network level, the SCD+, SCD-, and NC- groups all had small-world property. Among each of the whole brain network characteristics, statistically significant indicators included  $\lambda$  (significantly lower in the SCD+ group compared to the SCD- and NC- groups), global efficiency (higher in the SCD+ group compared to the NC group), and assortativity (lower in the SCD+ group compared to the SCD- and NC- groups). The  $\lambda$  was used to measure global information transmission capability of the network: a lower  $\lambda$  indicated higher information transfer speed between network nodes. In SCD+ patients, an increase in global efficiency value indicates enhanced brain network integration. Furthermore, lower assortativity suggests few similarities in the brain network connection of SCD+ patients. These results demonstrate that SCD occurs in the mild neuron injury stage with sufficient functional compensation,<sup>25</sup> which is consistent with previous results.<sup>26</sup> However, due to differences in study samples, our results are inconsistent with those of Xu et al.<sup>27</sup> Notably, SCD patients were not further stratified into APOE $\epsilon$ 4 carriers or non-carriers Xu et al,<sup>27</sup> which may explain the discrepancy. Indeed, the presence or absence of the APOE $\epsilon$ 4 allele may affect disease progression. APOE $\epsilon$ 4 disrupts nerve signals in

specific regions by affecting cholesterol metabolism, A $\beta$  phagocytosis, neurotrophic support, and synaptic pruning of astrocytes, and early brain activities adapt to demand and induce recombination of the brain rsFC.

When comparing intracephalic node characteristics in the functional network between the SCD+ group and the SCD- and NC- groups, the SCD+ group had lower local efficiency at the level of the left superior occipital gyrus node, part of the anterior lateral occipital complex (aLOC) that has been implicated in the primary sensory processing and coding of object shape.<sup>28</sup> Koolschijn et al<sup>29</sup> increased glutamic acid and subsequently reduced  $\gamma$ -aminobutyric acid via transcranial direct current stimulation (tDCS) to quantify the concentration of two key metabolites in this region using magnetic resonance spectroscopy (MRS). By recording the reduction of  $\gamma$ -aminobutyric acid and the increase of glutamic acid in aLOC before and after tDCS, Koolschijn et al<sup>29</sup> found that the excitation/inhibition imbalance in the aLOC region damages hippocampal memory discrimination. Interestingly, the SCD+ group had lower local efficiency at the level of the superior occipital gyrus, and SCD patients with the APOE $\epsilon$ 4 allele showed significantly lower local efficiency than SCD patients and NCs. This reduction in local efficiency resulted in lower information transmission capability between network nodes and broke the original excitement/inhibition balance in the aLOC region, affecting hippocampal memory discrimination and causing memory decline.

The efficiency at the posterior cingulate cortex node was increased in the SCD+ group. As part of posterior medial cortex, the posterior cingulate cortex has high connectivity anatomically and a high basal metabolic rate; it is a central component of the DMN.<sup>30</sup> The posterior cingulate cortex has a strong connectivity with DMN and connects with the frontal-parietal region to mediate cognition and the parahippocampal gyrus to aid in memory formation. In a study on directed functional connectivity, Yu et al<sup>31</sup> report enhanced directed connectivity from the whole brain to the posterior cingulate cortex in AD and MCI patients. Notably, patients in the SCD+ group presented with higher local node efficiency and stronger information transmission capabilities between network nodes, which may affect local metabolism in the presence of the APOE $\epsilon$ 4 allele. To overcome the inefficiency of the network, the brain compensatively increases its neural activities to meet demand. The posterior cingulate cortex affects connectivity in the DMN, frontal-

parietal region, and parahippocampal gyrus. Indeed, in early neuron injury models, inter-node information requires compensatory enhancement to maintain cognitive function.

The local efficiency at the level of the putamen was higher in the SCD+ group. Sekutowicz et al<sup>32</sup> observed that the activation of the right putamen during cognitive task switching was associated with bistable perceptual switching. Furthermore, Durstewitz et al<sup>33</sup> reported that basal ganglion activity increased cognitive flexibility through selective and dynamic gating functions and accelerated the renewal of the prefrontal cortex representation. Finally, in a study on amnesic MCI, Cai et al<sup>34</sup> found that the FC between the putamen and hippocampus was reduced, and amnesic MCI rapidly progressed into AD. In SCD patients with the APOE $\epsilon$ 4 allele, prefrontal lobe characteristics show compensatory alterations with enhanced local efficiency of bilateral putamen.

DMN is roughly divided into three parts: dorsal and ventral prefrontal cortex, posterior cingulate cortex, and adjacent precuneus plus lateral parietal cortex.<sup>35</sup> In SCD patients, DMN rsFC appears heterogeneous.<sup>16,36–42</sup> Davis et al<sup>43</sup> proposed that functional compensation mechanisms of aging shift and aging actually reduces inactivation of the posterior midline cortex, but increases inactivation of the medial frontal cortex. Our study is consistent with this model, as rsFC was increased in the posterior cingulate cortex but decreased in the dorsolateral superior frontal gyrus. Furthermore, in complex, non-linear dynamic diseases, temporal and spatial changes in the cross-brain network may gradually evolve from the “in-network stage” to the “whole network stage”, and finally to the “multi-network compensation stage”.<sup>15</sup>

rsFC abnormalities in the SCD+ group were similar to those of MCI and AD patients, as manifested in dysfunctional brain regions; however, local efficiency and connectivity also increased or decreased, respectively, as did the compensatory function between each node and the whole brain network before SCD+ progressed to MCI or AD. rsFC abnormalities in the SCD+ group were also markedly more severe than those in the SCD– and NC groups, which might be correlated to APOE $\epsilon$ 4 presence. Staffaroni et al<sup>44</sup> found no notable differences in rsFC longitudinal trajectory at baseline or DMN in the subjective memory of patients with APOE $\epsilon$ 4. However, Chiesa et al<sup>15</sup> reported that the increase of rsFC was slower at the levels of the frontal and prefrontal lobes in subjective memory complaints with the APOE $\epsilon$ 4 allele. Here, we report that rsFC was altered slightly in the SCD– group, indicating that SCD patients may have

a minor nerve injury. However, the degree of rsFC change in the SCD+ group was even greater and associated with the APOE $\epsilon$ 4 allele in cholesterol metabolism and A $\beta$  phagocytosis of astrocytes in the brain, and the exacerbation of A $\beta$  deposition- and tau-induced neurodegeneration and atrophy to aggravate nerve injury.

APOE $\epsilon$ 4 affects the functional brain network in patients with SCD. The SCD+ group demonstrated similar changes in compensatory whole brain network activity and intracerebral node characteristics in patients with MCI and AD dementia. Clinically, Hong et al<sup>45</sup> compared baseline characteristics between stable and progressive SCD to predict the relevant factors for SCD progression: presence of the APOE $\epsilon$ 4 allele was one of the strongest predictors of the transformation from SCD to objective cognitive impairment. Dik et al<sup>46</sup> also found that in elderly individuals, the effects of SCD and the presence of the APOE $\epsilon$ 4 allele were additive, and the cognitive decline of subjects with both factors was twice that of subjects with one or neither. Furthermore, in a neuroimaging study, Striepens et al<sup>47</sup> measured the volume of hippocampus, entorhinal cortex, and amygdala by structural MRI and found that the negative impact of APOE $\epsilon$ 4 on episodic memory and hippocampal volume supported SCD as the preclinical stage of AD. Finally, the longitudinal trajectory of DMN in SCD patients in a voxel study<sup>15</sup> observed wide DMN FC changes at the levels of the frontal lobe, posterior lobe, and right hippocampus, but slow FC increases in the frontal lobe in APOE $\epsilon$ 4 carriers.<sup>13</sup>

In a cross-sectional study, the current experiment did not evaluate whether APOE $\epsilon$ 4-related changes in brain functions are directly associated with future occurrence of MCI or AD. Since there is currently no clear definition of SCD, SCD in this study was based on individual memory complaints, and represented the subjective memory complaint group (SMC) well, but not overall SCD.<sup>48</sup> Since the ADNI database included fewer SCD patients who had neuropsychological assessment, CSF biomarkers, APOE genotyping information, and rs-fMRI data, our sample size was relatively small, which affected the reliability of the results. In future studies, a larger sample size and stricter quality control standards should be used to improve the reliability of results. AD pathological markers used in this study were obtained from CSF but are still an indirect way to reflect AD pathology. Therefore, in future studies, the addition of live animal models and the confirmation with molecular imaging and molecular biology data will help to further research of the pathophysiological mechanism and changes in MRI indicators. Although there



was no difference in neuropsychological assessment among groups in this study, future studies should include more detailed neuropsychological scores, such as anxiety scale.

In this study, graph theory was used to analyze rsFC changes in SCD patients with the APOE $\epsilon$ 4 allele and determine whether APOE $\epsilon$ 4 affects the functional brain network of SCD patients. Although the rsFC was highly heterogeneous, we found that SCD patients with the APOE $\epsilon$ 4 allele demonstrate abnormal DMN connectivity and compensatory effects at the levels of the bilateral putamen and left superior occipital gyrus. Our results indicate that APOE $\epsilon$ 4 affects the functional brain network of patients with SCD, and the relationship between APOE $\epsilon$ 4 biomarkers and pathological cognitive decline has been reliably reported.<sup>49</sup> The APOE $\epsilon$ 4 collection method is fast, noninvasive, and relatively low-cost,<sup>50</sup> and the presence of the APOE $\epsilon$ 4 allele may be a tool to identify cognitive decline in SCD patients in clinical practice.

## Conclusion

This study utilized graph theory to study the rsFC of SCD patients with APOE $\epsilon$ 4 in an effort to explore the effect of APOE $\epsilon$ 4 on functional brain networks of SCD patients. We found that the SCD+ group had increased compensatory information transfer speed and enhanced integration capability, with a lower AUC of LP,  $\lambda$ , and assortativity, but higher global efficiency. The SCD+ group also has high heterogeneity in intracerebral node characteristics, mainly in the DMN, left superior occipital gyrus, and bilateral putamen. Therefore, we believe that APOE $\epsilon$ 4 affects the functional brain network in patients with SCD and may be used as a potential indicator of SCD progress.

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## Disclosure

The authors report no conflicts of interest in this work, and the data accessed comply with relevant data protection and privacy regulations.

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