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Imbalanced hippocampal functional networks associated with remitted geriatric depression and apolipoprotein E ϵ 4 allele in nondemented elderly: a preliminary study

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Abstract

Background—Apolipoprotein E (APOE) ϵ 4 allele and a history of geriatric depression are confirmed risk factors of Alzheimer's disease (AD). Coexistence of both factors could notably enhance the risk of cognitive impairment in nondemented elderly. However, neural basis of the association remains unclear.

Methods—Thirty-one remitted geriatric depression (RGD) patients and 29 cognitively normal subjects were recruited and underwent resting-state functional MRI scans. They were further divided into four groups according to their APOE genotypes. Hippocampal seed-based network analysis and two-way factorial analysis of covariance were employed to detect the main effects and interactive effects of RGD and APOE ϵ 4 allele on the hippocampal functional connectivity (HFC) networks. Partial correlation analysis was applied to examine the cognitive significance of these altered HFC networks.

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Contributors

Dr. Zhijun Zhang had full access to all of the study data and took responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Hao Shu and Dr. Chunming Xie were responsible for analyzing data and composing the manuscript. Dr. Yonggui Yuan and Dr. Jiayong You were in charge of recruiting subject, MRI scanning and APOE genotype testing. Dr. Shi-Jiang Li and Dr. Feng Bai participated in analyzing the data and interpreting the results. Dr. Lingjiang Li assisted with the study design. All authors contributed to and have approved the final manuscript.

Declaration of conflict interest

None of the authors have a conflict of interest related to this study.

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Results—The HFC networks of RGD patients were decreased in the dorsal frontal and increased in the right temporal-occipital regions. For APOE $\epsilon 4$ carriers, the HFC networks were reduced primarily in medial prefrontal regions and enhanced in the bilateral insula. Additionally, when both factors coexisted, the left HFC network was significantly disrupted in the dorsal anterior cingulate cortex and increased in somatomotor and occipital regions. Importantly, the extent of network alterations was linked to inferior cognitive performances in RGD patients and APOE $\epsilon 4$ carriers.

Limitations—The small sample size may limit the generalizability of our findings.

Conclusions—RGD and APOE $\epsilon 4$ allele, and their interaction, are associated with the imbalanced HFC network, which may contribute to cognitive deterioration for subjects with a high risk of AD.

Keywords

Remitted geriatric depression; Apolipoprotein E $\epsilon 4$ allele; Hippocampus; Functional connectivity; Functional magnetic resonance imaging; Resting state

1. Introduction

Geriatric depression has been the subject of great concern recently, as researchers believe it increases the risk of patients progressing to dementia, even when the affective symptoms are relieved after effective antidepressant treatments (Byers and Yaffe, 2011). Longitudinal studies demonstrated persistent cognitive impairment or a significantly elevated incidence of Alzheimer's disease (AD) in remitted geriatric depression (RGD) patients (Wilson et al., 2002). Recently, neuroimaging studies identified structural or functional abnormalities in RGD patients. These include hippocampal atrophy, as well as disrupted functional activity in regions susceptible to AD (Steffens et al., 2011; Wang et al., 2012a). Commonalities also have been evident between amnesic mild cognitive impairment (aMCI) and RGD patients (Bai et al., 2012a). These studies initially revealed the specific neural substrates linking RGD with cognitive impairment in the elderly. Additionally, the influence of genetic factors on human cognitive functions at the neural system level has been demonstrated (Meyer-Lindenberg, 2011). Understanding whether and how the genetic risk factor affects the relationship between RGD and cognitive impairment would provide insight into the mechanism of cognitive deterioration in elderly.

Apolipoprotein E (APOE) $\epsilon 4$ allele is the established genetic risk factor of AD that could elevate the incidence and advance the age of onset in a dose-dependent way (Seripa et al., 2009). Neuroimaging studies identified the functional and structural patterns of APOE $\epsilon 4$ allele in the AD-spectrum (Reiman et al., 2005; Wolk and Dickerson, 2010). While the association between APOE $\epsilon 4$ allele and the development of geriatric depression remains controversial (Steffens et al., 2003; Yen et al., 2007), it has been suggested that the coexistence of geriatric depression history and APOE $\epsilon 4$ allele would disrupt neurological function and lower an individual's cognitive reserve capacity, and thus, notably increase the risk of cognitive impairment and the incidence of AD in nondemented elderly (Corsentino et al., 2009; Yuan et al., 2010). Although these studies have demonstrated that APOE $\epsilon 4$ allele

may exacerbate the persistent detrimental influence of geriatric depression on the cognitive function, the neural basis underlying the complex relationship remains to be resolved.

The hippocampus plays a critical role in regulating high-order cognitive function, including memory and mood processing (LaBar and Cabeza, 2006). It is one of the earliest brain regions damaged by AD neuropathology (Lee et al., 2003). Neuroimaging studies demonstrated hippocampal abnormalities in the predementia stage of AD. These include structural atrophy or functional alterations in aMCI patients (Bai et al., 2009b; Sperling et al., 2010) and cognitively normal APOE $\epsilon 4$ carriers (Trachtenberg et al., 2012). Moreover, for aMCI patients, the contribution of APOE $\epsilon 4$ allele to the hippocampal atrophy has been further demonstrated (Lo et al., 2011). However, in the context of geriatric depression, whether and how APOE $\epsilon 4$ allele associates with hippocampal abnormalities is seldom concerned to date. To our knowledge, only two studies indicated structural alterations of hippocampi in geriatric depression patients carrying APOE $\epsilon 4$ allele (Kim et al., 2002; Qiu et al., 2009). It remains unclear how the functional couplings of hippocampi alter under the effects of APOE $\epsilon 4$ allele and geriatric depression, especially when the affective symptoms are relieved. Recently, researchers demonstrated that the resting-state functional connectivity MRI (R-fcMRI) technique, as a task-independent imaging modality, is a powerful tool in studying the intrinsic functional connections between anatomically distinct brain regions within specific networks and investigating the neural basis of interindividual phenotypic variations, thereby showing great promise as an imaging biomarker in preclinical and clinical conditions (Zhang and Raichle, 2010). In the present study, the R-fcMRI method utilizing the bilateral hippocampi as seed regions will be employed to examine the neural substrates responsible for linking RGD and APOE $\epsilon 4$ allele in nondemented elderly.

Therefore, the first objective of this study was to investigate the neural substrates implicated in the main effects, in addition to the interactive effects, of RGD and APOE $\epsilon 4$ allele on the intrinsic hippocampal functional connectivity (HFC) networks, using the R-fcMRI approach. Secondly, we will examine the cognitive significance of the abnormal HFC networks by partial correlation analysis in nondemented elderly.

2. Methods

2.1. Subjects

Thirty-seven RGD patients were recruited from Affiliated Nanjing Brain Hospital, Nanjing Medical University (Nanjing, China). Thirty-one cognitively normal control (NC) subjects were recruited through community health screening. The inclusion and exclusion criteria for RGD patients were described previously (Bai et al., 2012a). Briefly, they met: (1) they had previously met the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV) criteria for major depression disorder and had remitted for more than six months before enrollment, (2) the age of onset was over 60, (3) the duration of the illness was less than five years and the period of remaining anti-depressant medication-free was more than three months, (4) Hamilton Depression Rating Scale (HDRS) scores were lower than 7, the Mini-Mental State Examination (MMSE) scores were higher than 24 that is widely used in screening dementia with limitation in identifying MCI (Mitchell, 2009), (5) absence of any other axis I psychiatric or neurological illness and medical conditions impairing cognitive

function, (6) no history of receiving electroconvulsive therapy, (7) absence of gross structural abnormalities in MRI images. All RGD patients were examined when they were in remission. Normal controls were physical healthy, with no history of severe illness or substance abuse and no first-degree family history of psychiatric illness. They also met items (4) and (7) of the inclusion criteria of RGD patients. Written informed consent was obtained and the study protocol was approved by the Research Ethics Committee of Zhongda Hospital affiliated to Southeast University. Six RGD and two NC subjects were excluded because of excessive motion artifacts (i.e., exceeding 3 mm of maximum displacement in any direction or 3° of angular motion) or incomplete image scans. Hence, 31 RGD and 29 NC subjects were left for further analysis.

2.2. Neuropsychological tests

Two trained psychiatrists (Y Yuan and J You) administered neuropsychological battery tests to assess the subjects' cognitive function. The battery consists of auditory verbal learning test-delayed recall (AVLT-DR), Rey–Osterrieth complex figure test (CFT) with its immediately recall (CFT-IR), symbol digit modalities test (SDMT), trail-making tests A and B (TMT-A and TMT-B) and digit span test (DST), which covered episodic memory, working memory, visuospatial, perceptual speed and executive domains.

2.3. APOE genotyping

Each subject's genomic DNA was extracted from 250ul EDTA-anticoagulated blood, using a DNA direct kit (Omega Bio-Tek, USA). A polymerase chain reaction-based restriction fragment length polymorphism assay was applied to detect the APOE genotype, according to the work by Wenham and colleagues (Wenham et al., 1991). Thus, the subjects were further divided into four groups according to their APOE genotypes, as shown in Table 1. Each group was identified as RGD-APOE4+, RGD-APOE4–, NC-APOE4+ and NC-APOE4– hereafter.

2.4. MRI data acquisition

Images were performed in a General Electric 1.5T scanner (General Electric Medical Systems) with a homogeneous birdcage head coil. The participants were instructed to relax and close their eyes, and their ears were occluded during the scan. Resting-state functional images consisting of 30 contiguous axial slices and 142 volumes were acquired by gradient-recalled echo-planar imaging (GRE-EPI) sequence: repetition time (TR) = 3000ms; echo time (TE) = 40ms; flip angle (FA) = 90°; acquisition matrix = 64 × 64; field of view (FOV) = 240 × 240mm; thickness = 4.0mm; gap = 0mm. High-resolution T1-weighted axial images covering the whole brain were acquired by 3D spoiled gradient-echo (SPGR) sequence as below: TR = 9.9ms; TE = 2.1ms; FA = 15°; acquisition matrix = 256 × 192; FOV = 240 × 240mm; thickness = 2.0mm; gap = 0mm. Additionally, routine axial T2-weighted images were obtained to rule out subjects with cerebral infarction or other lesions.

2.5. Image preprocessing

Imaging data was analyzed by Data Processing Assistant for Resting-State fMRI (DPARSF) V2.0 (<http://www.restfmri.net/forum/DPARSF>). The first 10 volumes of the scanning

session were discarded to allow for T1 equilibration effects. Then, the procedures of slice timing and realignment were performed to correct for the time differences in acquisition among slices within one volume and the motion effects (six-parameter rigid body) during the scan. The resulting images were spatially normalized into a standard stereotaxic space with a 12-parameter affine approach and an EPI template image, and then resampled to 3×3×3 mm voxels. Six head motion parameters, white matter (WM), cerebrospinal fluid (CSF) and global signals were removed as covariates of no interest to minimize possible confounding effects. Ultimately, linear trend removing and band-pass filtering (0.01–0.08 Hz) were performed to accomplish the procedure of preprocessing.

2.6. Functional connectivity analysis

To create seeds for the connectivity analysis, bilateral hippocampi regions were extracted from the automated anatomical labeling (AAL) template separately. Following this, the extracted seed regions were resampled to the same space as the functional data. For each subject, a mean time series of each hippocampus was utilized as the seed time course respectively. Pearson cross-correlation analysis was applied between the seed time course and the time course of whole-brain voxels. A Fisher's Z-transformation was then used to improve the normality of the correlation coefficients [$Z=0.5*\ln(1+r)/(1-r)$]. Finally, these voxelwise Z values were smoothed with a 4-mm Gaussian kernel to correspond with series studies that we previously reported (Bai et al., 2009a; Wang et al., 2012b). The individual maps of bilateral HFC networks were obtained.

2.7. Voxelwise-based morphometry correction

To ensure that the differences of functional connectivity (FC) were not driven by the anatomical differences between groups, voxelwise gray matter (GM) volume was included as a covariate in the functional data analysis (Bai et al., 2011a; Bai et al., 2011b). First, the individual GM volume maps were obtained with the toolbox of voxel-based morphometry 8 (VBM8) (<http://dbm.neuro.uni-jena.de/vbm/>). Then, the GM volume maps were transformed into the same final working space as the functional data through affine linear registration. Third, the obtained GM volume maps were smoothed with 4-mm Gaussian kernel to match the smoothness of functional data, considering that the VBM images can be sensitive to the smoothing kernel size. Finally, the resultant voxelwise GM values were regressed out as the nuisance regressor from the FC values to control the influence of GM volume on the FC strength. The voxelwise GM volume correction was performed for each subject.

2.8. Statistical analysis

2.8.1. Demographic and neuropsychological data—One-way analysis of variance (ANOVA) and Fisher's exact probability tests (only applied in gender comparison for the sample size of male < 5 in two groups) were used to compare demographic data and neuropsychological performances among groups with the statistical significance of $p < 0.05$. Post hoc tests by Tukey-Kramer analysis were used to reveal the source of ANOVA difference.

2.8.2. Group-level intrinsic connectivity analysis—The individual HFC networks maps were grouped together respectively for each group. Then, the patterns of left and right

HFC networks for each group were obtained by a random-effects one-sample *t*-test according to the AlphaSim correction based on Monte Carlo simulation algorithm ($\alpha=0.05$, voxelwise $p<0.05$, cluster sizes $>2079\text{mm}^3$) (<http://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf>). To analyze the main effects and interactive effects of RGD and APOE $\epsilon 4$ allele on the bilateral HFC networks, a two-way factorial analysis of covariance (ANCOVA: RGD $\times$ APOE4 allele) was performed with AlphaSim correction ($\alpha=0.05$, voxelwise $p<0.05$, cluster sizes $>2079\text{mm}^3$), controlling for age, gender and education years. Subsequently, numerical representations of the mean FC strength of each significant cluster were shown to reflect the alterations of HFC networks among groups.

2.8.3. Correlation analysis between HFC network alteration and cognitive performance

—To further identify the cognitive significance of the altered HFC networks, the averaged FC strength of each significant region observed in the ANCOVA analysis was extracted respectively. Then, a partial correlation analysis was employed between the averaged FC strength of each region and the neuropsychological performance in RGD patients or APOE $\epsilon 4$ carriers. To increase statistical power by reducing random variability, a composite score analysis was utilized, as previously introduced (Xie et al., 2012). First, the raw scores from each subject's test were transformed to *Z* scores with the reference to mean and standard deviation of each test for all subjects. Second, all neuropsychological tests were grouped into five cognitive domains and the related composite scores were calculated by averaging the *Z* scores of the individual tests according to the following divisions: Episodic Memory (two tests, including AVLT-DR and CFT-IR), Working Memory (DST), Visuospatial Function (CFT), Perceptual Speed (two tests, including SDMT and TMT-A) and Executive Function (TMT-B). The statistical procedure utilized SPSS 17.0 software (SPSS Inc., Chicago, Ill., USA), controlling the effects of age, gender, education years and group. Bonferroni correction for multiple comparisons was used with the significance level set at $p<0.05/5=0.01$ as five composite scores participated in the analysis.

3. Results

3.1. Demographic information and cognitive performance

Demographic and neuropsychological characteristics of subjects are shown in Table 1. No significant difference was found among the four groups, except for age ($F=4.14$, $p=0.01$) and the level of perceptual speed ($F=6.56$, $p=0.001$) and executive function ($F=3.61$, $p=0.02$). Post hoc tests further demonstrated that the age in the NC-APOE4 $^-$ group was significantly older than that in the RGD-APOE4 $^+$ group ($t=3.27$, Tukey-Kramer corrected $p=0.01$). Therefore, age was included as covariate for all statistical analyses. Moreover, compared with the NC-APOE4 $^-$ group, significantly impaired cognitive functions in perceptual speed were observed in the RGD-APOE4 $^-$ ($t=-4.23$, Tukey-Kramer corrected $p<0.001$) and RGD-APOE4 $^+$ groups ($t=-2.84$, Tukey-Kramer corrected $p=0.03$). Additionally, the RGD-APOE4 $^-$ group showed inferior executive performance compared with the NC-APOE4 $^-$ group ($t=-2.83$, Tukey-Kramer corrected $p=0.03$).

3.2. Group-level HFC network patterns

Each HFC network pattern is composed of a positive network and a negative network, which appeared similar in four groups ($p < 0.05$, AlphaSim corrected). In the left HFC network, there was positive functional connectivity associated with the bilateral parahippocampal gyrus (PHG), thalamus, cingulate cortex, medial prefrontal cortex (MPFC), lateral temporal lobe, insula and left somatomotor area, while negative functional connectivity was primarily located in the bilateral lateral frontal areas, parietal and occipital regions. Similarly, the right HFC network showed significant positive connectivity with the bilateral PHG, thalamus, posterior cingulate cortex (PCC), lateral temporal lobe, insula and right somatomotor area, while the negative HFC network was mainly involved with the bilateral lateral frontal regions, as well as parietal and occipital regions. The patterns of bilateral HFC networks for the four groups are shown in the supplementary Figure S1 and Figure S2.

3.3. Main effects of RGD and APOE $\epsilon 4$ allele on the bilateral HFC networks

As illustrated in Figure 1 and Table 2, for the left HFC network, RGD patients showed: 1) decreased positive HFC to left MPFC and middle frontal gyrus (MFG); 2) increased negative HFC to right MFG/superior frontal gyrus (SFG); 3) decreased negative HFC to right inferior occipital gyrus (IOG)/lingual gyrus (LG). For the right HFC network, RGD patients showed: 1) decreased positive HFC to left MFG and somatomotor area; 2) decreased negative HFC to right superior parietal lobule (SPL); 3) increased positive HFC to right posterior middle temporal gyrus (pMTG), LG and cuneus.

Similarly, as described in Figure 2 and Table 2, we found APOE $\epsilon 4$ carriers showed a disrupted HFC network in diffuse regions compared with noncarriers, except the bilateral insula. Specifically, for the left HFC network, APOE $\epsilon 4$ carriers showed: 1) decreased positive HFC to bilateral MPFC/anterior cingulate cortex (ACC) regions; 2) decreased negative HFC to right supramarginal gyrus (SMG); 3) increased positive HFC to bilateral insula. Similarly, for the right HFC network, APOE $\epsilon 4$ carriers exhibited: 1) decreased positive HFC network in multiple areas, including the bilateral MPFC, inferior temporal gyrus (ITG) and right inferior frontal gyrus (IFG); 2) decreased negative HFC to the left inferior parietal lobule (IPL) and 3) increased positive HFC to left insula.

3.4. Interactive effects of RGD and APOE $\epsilon 4$ allele on the left HFC network

The interactive effects of RGD and APOE $\epsilon 4$ allele were found in the bilateral dorsal ACC/MPFC, somatomotor area and right IOG regions that are connected to the left hippocampus. These interactive effects indicated opposite directions of the influence of APOE $\epsilon 4$ allele between the NC and RGD group. Specifically, the coexistence of RGD and APOE $\epsilon 4$ allele synergistically disrupted the functional connectivity of the left hippocampus to the bilateral dorsal ACC/MPFC regions. Conversely, enhanced connections of left HFC network were observed in the other two regions for RGD patients carrying APOE $\epsilon 4$ allele, as shown in Figure 3 and Table 2.

3.5. Cognitive significance of the altered HFC networks

With the partial correlation analysis controlling the effects of no interest including group, age, gender and education years, we observed that the extent of the alteration in HFC networks was associated with lower cognitive performance for both RGD patients and APOE $\epsilon 4$ carriers. First, as Figure 4A illustrates, for RGD patients, the decreased positive FC of the right hippocampus to left somatomotor area (R5 in Figure 1) positively correlated with the episodic memory scores, indicating that the weaker the FC is, the worse the episodic memory performance ($R^2=0.34$, $p=0.001$). Interestingly, the decreased negative FC between the left hippocampus and right IOG/LG (R4 in Figure 1) was found to negatively correlated with visuospatial scores, which means the higher absolute FC is, the more inferior the visuospatial function ($R^2=0.22$, $p=0.008$). Second, for APOE $\epsilon 4$ carriers, the decreased positive FC of the right hippocampus to bilateral MPFC/ACC (R5 in Figure 2) positively correlated with working memory scores ($R^2=0.60$, $p=0.0002$), which means the lower the FC is, the worse the working memory performance, as shown in Figure 4B.

4. Discussion

In this study, we found that both RGD and APOE $\epsilon 4$ allele, as well as their interaction, could destabilize the HFC networks. First, for RGD patients, their bilateral HFC networks were reduced in the dorsal frontal regions and enhanced in the right temporal-occipital regions. Second, we observed that the APOE $\epsilon 4$ allele decreased the FC strength of HFC networks primarily in the MPFC regions and increased it mainly in the bilateral insula. Third, investigation on the interaction of both factors found the functional coupling of the left HFC network was reduced in the dorsal ACC and enhanced in the bilateral somatomotor and right occipital regions when both factors coexist. Importantly, we further observed the cognitive significance of the disturbed HFC networks, indicating greater alterations of HFC networks were associated with poorer cognitive performances for both RGD patients and APOE $\epsilon 4$ carriers. In all, our results indicated the imbalance of HFC networks in the context of RGD and APOE $\epsilon 4$ allele, and further implied their contribution to cognitive deterioration in nondemented elderly.

The imbalanced HFC network for RGD patients could be divided into two parts. First, we observed the disconnection between the hippocampi and dorsal frontal regions. Frontal-limbic network dysfunction has been demonstrated in depression across the lifespan (Alexopoulos, 2002). Specifically, decreased activities in the dorsal part of the frontal-limbic network have been conceptualized as the failure of top-down control to the ventral emotional part of the network that contributes to a depression episode (Ray and Zald, 2012). In geriatric depression, the gray-matter atrophy and disrupted white-matter integrity in frontal-limbic areas also have been identified (Murphy et al., 2007; Steffens et al., 2002). Furthermore, RGD patients with persistent cognitive impairment showed greater decreased activity in the dorsal part of frontal-limbic network, compared with those without cognitive impairment (Wang et al., 2012a). From the perspective of the cognitive role, the dorsal frontal areas are attributed with responsibility of high-order cognitive function including attention and executive domains. These have been demonstrated as the core cognitive deficits of geriatric depression and were also observed in our study, indicating the link

between aberrant frontal activity and cognitive impairment for RGD patients (Sheline et al., 2006). On the other hand, we also found increased positive right HFC and decreased negative left HFC to right temporal-occipital regions in RGD patients. Recently, Gee et al. demonstrated that positive connectivity strength was greater within hemisphere, while negative connectivity strength was stronger between hemispheres (Gee et al., 2011). Hence, such hemisphere asymmetry in the NC group could affect the direction of alteration when compared with the RGD group. Moreover, both the left and right hippocampi showed positive functional connectivity to right temporal-occipital regions in RGD patients, suggesting that RGD facilitated greater functional coupling between the bilateral hippocampi and right temporal-occipital regions. Taken together, our findings indicated that RGD patients showed disarranged HFC networks even when their emotional symptoms were relieved after effective antidepressant treatment.

Additionally, the disturbed HFC networks also have been demonstrated in APOE $\epsilon 4$ carriers. On the one side, the disconnection of bilateral HFC networks was observed, especially in bilateral MPFC/ACC regions. These regions have been identified as one of the major parts of the default mode network (DMN), and have reciprocal connections with the hippocampal-related limbic network (Catani et al., 2013). Both DMN and hippocampal-related limbic networks are essential for subjects to successfully perform memory tasks. They have been consistently impaired across the AD-spectrum (Sorg et al., 2007; Wang et al., 2006). Moreover, DMN disconnection in elderly cognitively normal $\epsilon 4$ carriers has been demonstrated (Sheline et al., 2010), indicating that the aberrant functional network may contribute to the cognitive deterioration for subjects with high risk of AD. On the other hand, we simultaneously found the enhanced HFC networks in the bilateral insula. The insula, especially the anterior part, has been noted as a hub of the salience network, and it plays a key role in switching between the DMN and central-executive network across various states (Menon and Uddin, 2010). Interestingly, the enhanced activity of the salience network always co-occurs with the decreased activity of the DMN in the early stage of AD (Brier et al., 2012). Moreover, our recent studies demonstrated the disrupted intrinsic connectivity of the insula, as well as the abnormal dynamic modulation of the DMN and task-positive network between the resting and the task-related state in aMCI patients (Bai et al., 2012b; Xie et al., 2012). These studies suggested the contribution of abnormal insula activity to the cognitive deterioration in the predementia stage. Taken together, the coexistence of decreased HFC networks in bilateral MPFC and enhanced HFC networks in bilateral insula in our findings indicated that the APOE $\epsilon 4$ allele is associated with an imbalanced HFC network, which may contribute to cognitive deterioration for $\epsilon 4$ carriers in future.

Furthermore, the interactive effect of RGD and APOE $\epsilon 4$ allele was identified in this study. Recently, the synergistic effect of APOE $\epsilon 4$ allele and depressive symptoms on persistent cognitive deterioration was widely demonstrated in studies, including two with an East Asian sample (Kim et al., 2011; Niti et al., 2009). Structural studies further found hippocampal abnormalities in depressive patients with APOE $\epsilon 4$ allele that may contribute to AD conversion (Kim et al., 2002; Qiu et al., 2009). Similarly, in the current study, the imbalanced left HFC network was indicated when the factors of RGD and APOE $\epsilon 4$ allele interacted. First, we observed the disconnection of left hippocampus to bilateral dorsal ACC

regions when both factors coexist. The dorsal ACC is believed to play a critical role in integrating affective and cognitive inputs to facilitate performing tasks demanding cognitive control (Shackman et al., 2011). Dysfunction of the ACC could persist in a disease-dependent manner in geriatric depression (Alexopoulos et al., 2008). Furthermore, Wang et al. recently proposed the causality between the deficits in dorsal ACC at baseline and the subsequent cognitive impairment in geriatric depression (Wang et al., 2012a). For studies on AD-spectrum, it was also demonstrated that dorsal ACC was associated with reduced metabolic activity, increased A β -deposition and faster conversion in APOE ϵ 4 carriers who convert to AD (Mosconi et al., 2004; Okello et al., 2009). Therefore, the disrupted left HFC to dorsal ACC in this study may imply the remarkably increased risk of cognitive deterioration for APOE ϵ 4 carriers with a history of geriatric depression. In addition, the increased FC strengths of the left hippocampus to the bilateral somatomotor area and right IOG were observed in RGD patients carrying APOE ϵ 4 allele. We speculate these enhanced effects could be interpreted as the brain recruiting extra resources in a compensatory way in responding to the damage in the dorsal ACC, and further be beneficial in maintaining cognitive function temporarily. Accordingly, these findings revealed the joint influence of RGD and APOE ϵ 4 allele on the HFC network, which may increase the susceptibility to cognitive deterioration for RGD patients with APOE ϵ 4 allele.

Importantly, the cognitive significances of the altered HFC networks were identified in this study. It is worth noting that the extent of network alterations were positively correlated with inferior cognitive performance in RGD patients and APOE ϵ 4 carriers. The greater the alteration of FC strength in the HFC network, the more inferior the cognitive performance, no matter what the direction of alteration. These findings indicated the contribution of the imbalanced HFC network to the cognitive impairment in RGD patients or APOE ϵ 4 carriers; it supported the network dysfunction hypothesis of AD. The network dysfunction hypothesis, initially proposed by Palop et al., holds that the abnormal network activity causally contributes to the cognitive impairments in the progression of AD (Palop et al., 2006). Specific functional network targeted by the AD pathogenesis have been indicated (Seeley et al., 2009). Moreover, Sanchez et al. recently demonstrated that the levetiracetam, an antiepileptic drug, could reverse the aberrant network activity, synaptic transmission dysfunction, hippocampal remodeling and memory deficits in human amyloid precursor protein transgenic mice (Sanchez et al., 2012). Similarly, the improved effect of levetiracetam on the task-related memory performance was also observed in aMCI patients (Bakker et al., 2012). These results strongly suggested the critical role of the abnormal network activity in the progression of AD. Corresponding to the network dysfunction hypothesis, our results indicate the imbalanced HFC networks may be the early contributor that increased the risk of AD onset for RGD patients and APOE ϵ 4 carriers.

5. Limitations

There are several limitations in our present study. First, this is a cross-sectional study with a relatively small sample size and this may limit the generalizability of our findings. Thus, the study with an independent large sample is essential to confirm the current results, and a longitudinal study is also necessary to validate the role of the imbalanced HFC network in cognitive deterioration in the future. Additionally, the brain is organized into a sophisticated

network involving various subnetworks intercommunicating with each other. Hence, investigation from a large-scale network perspective is necessary in future.

In this study, we demonstrated that RGD and APOE $\epsilon 4$ allele, as well as their interaction, were all involved in the imbalanced HFC networks. Furthermore, greater alterations of the HFC network were observed to associate with inferior cognitive performances in RGD patients and APOE $\epsilon 4$ carriers. Our findings, accordingly, indicated the contribution of imbalanced HFC network to the increased risk of AD for APOE $\epsilon 4$ carriers and subjects with a history of geriatric depression, and implied the importance of stabilizing network activity in resisting the cognitive deterioration for subjects with a high risk of AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Main effects of remitted geriatric depression (RGD) on the bilateral hippocampal functional connectivity (HFC) networks

($p < 0.05$, AlphaSim correction). **Left:** Brain regions with significant main effects of RGD on the left (top) and right (bottom) HFC network. Bright color indicates increased positive connectivity or decreased negative connectivity and blue color indicates decreased positive connectivity or increased negative connectivity. Color bar is presented with Z scores. **Right:** Numerical representation of significant main effects of RGD on the left (top) and right (bottom) HFC network (m is the Fisher's Z-transformed cross-correlation coefficient, same below). Error bars represent standard error of the mean of the Z values in each region.

Abbreviations: RGD: remitted geriatric depression. non-RGD: non-remitted geriatric depression. R1: left middle frontal gyrus; R2: left medial prefrontal cortex; R3: right middle frontal gyrus/superior frontal gyrus; R4: right inferior occipital gyrus/lingual gyrus; R5: left somatomotor area; R6: left middle frontal gyrus; R7: right superior parietal lobule; R8: right posterior middle temporal gyrus; R9: right lingual gyrus; R10: right cuneus.

Figure 2. Main effects of Apolipoprotein E (APOE) ϵ 4 allele on the bilateral hippocampal functional connectivity (HFC) networks ($p < 0.05$, AlphaSim correction). **Left:** Brain regions with significant main effects of APOE ϵ 4 allele on the left (top) and right (bottom) HFC network. Bright color indicates increased positive connectivity or decreased negative connectivity and blue color indicates decreased positive connectivity or increased negative connectivity. Color bar is presented with Z scores. **Right:** Numerical representation of significant main effects of APOE ϵ 4 allele on the left (top) and right (bottom) HFC network. Error bars represent standard error of the mean of the Z values in each region. Abbreviations: APOE4+: APOE ϵ 4 carriers. APOE4-: APOE ϵ 4 noncarriers. R1: bilateral medial prefrontal cortex/anterior cingulate cortex; R2: right supramarginal gyrus; R3: left insula; R4: right insula; R5: bilateral medial prefrontal cortex/anterior cingulate cortex; R6: right inferior temporal gyrus; R7: left inferior temporal gyrus; R8: right inferior frontal gyrus; R9: left inferior parietal lobule; R10: left insula.

Figure 3. Interactive effects of remitted geriatric depression (RGD) and Apolipoprotein E (APOE) ϵ 4 allele on the left hippocampal functional connectivity (HFC) network ($p < 0.05$, AlphaSim correction). **Left:** Brain regions with significant interactive effects on the left HFC network. The bright and blue colors indicate synergistic and inverse contributions of RGD and APOE ϵ 4 allele to the functional integration of the left HFC network, respectively. Color bar is presented with Z scores. **Right:** Numerical representation of significant interactive effects of RGD and APOE ϵ 4 allele on the left HFC network. Error bars represent standard error of the mean of the Z values in each region. Abbreviations: NC-APOE4-: APOE ϵ 4 noncarriers in normal control group. NC-APOE4+: APOE ϵ 4 carriers in normal control group. RGD-APOE4-: APOE ϵ 4 noncarriers in remitted geriatric depression group. RGD-APOE4+: APOE ϵ 4 carriers in remitted geriatric depression group. R1: bilateral dorsal anterior cingulate cortex/medial prefrontal cortex; R2: bilateral somatomotor area; R3: right inferior occipital gyrus.

Figure 4. Cognitive significances of the altered hippocampal functional connectivity (HFC) networks in remitted geriatric depression (RGD) patients (A) and Apolipoprotein E (APOE) ϵ 4 carriers (B)

(A) For RGD patients, the solid dots indicate RGD patients without APOE ϵ 4 allele, while the solid triangles denote RGD patients with APOE ϵ 4 allele. The decreased positive right HFC network in the left somatomotor area (R5 in Figure 1) associated with poorer performance in episodic memory (left part); the decreased negative left HFC network in the right inferior occipital gyrus/lingual gyrus (R4 in Figure 1) linked to worse visuospatial function (right part). (B) For APOE ϵ 4 carriers, the hollow dots indicate APOE ϵ 4 carriers in normal control group, while the hollow triangles denote APOE ϵ 4 carriers in RGD group. The decreased positive right HFC network in bilateral medial prefrontal cortex/anterior cingulate cortex (R5 in Figure 2) is associated with inferior working memory performance. The above results were obtained by the partial correlation analysis controlling the effects of no interest including group, age, gender and education years. Abbreviations: Hippo: hippocampus; SMA: somatomotor area; IOG/LG: inferior occipital gyrus/lingual gyrus; MPFC/ACC: medial prefrontal cortex/anterior cingulate cortex; B, bilateral.

Table 1

Clinical and neuropsychological data for all subjects.

	NC group		RGD group		F or χ^2	p
	APOE $\epsilon 4+$ (n=7)	APOE $\epsilon 4-$ (n=22)	APOE $\epsilon 4+$ (n=11)	APOE $\epsilon 4-$ (n=20)		
Age (years)	70.14 $\pm$ 4.88	71.81 $\pm$ 3.81	66.73 $\pm$ 3.52 ^a	68.60 $\pm$ 4.73	4.14	0.01 ^{\$} *
Gender (M/F)	3/4	10/12	3/8	8/12	1.11	0.82%
Education (years)	15.00 $\pm$ 3.42	14.52 $\pm$ 2.64	14.36 $\pm$ 1.80	14.30 $\pm$ 1.75	0.17	0.92 ^{\$}
Episodic Memory	0.14 $\pm$ 0.53	0.23 $\pm$ 0.70	-0.27 $\pm$ 0.64	-0.15 $\pm$ 0.88	1.55	0.21 ^{\$}
AVLT-DR	0.31 $\pm$ 0.52	0.37 $\pm$ 0.86	-0.22 $\pm$ 1.19	-0.39 $\pm$ 1.04	2.62	0.06 ^{\$}
CFT-IR	-0.02 $\pm$ 0.92	0.09 $\pm$ 0.94	-0.32 $\pm$ 1.12	0.09 $\pm$ 1.06	0.46	0.71 ^{\$}
Working Memory						
DST	-0.24 $\pm$ 1.23	0.21 $\pm$ 0.70	0.05 $\pm$ 1.05	-0.18 $\pm$ 1.18	0.67	0.58 ^{\$}
Visuospatial Function						
CFT	0.29 $\pm$ 0.29	0.28 $\pm$ 0.30	-0.31 $\pm$ 0.97	-0.23 $\pm$ 1.50	1.50	0.23 ^{\$}
Perceptual Speed	0.11 $\pm$ 0.52	0.44 $\pm$ 0.57	-0.23 $\pm$ 0.92 ^a	-0.40 $\pm$ 0.57 ^b	6.56	0.00 ^{\$} *
SDMT	0.12 $\pm$ 0.75	0.38 $\pm$ 0.79	-0.26 $\pm$ 1.13	-0.32 $\pm$ 1.11	2.17	0.10 ^{\$}
TMT-A	0.09 $\pm$ 0.96	0.50 $\pm$ 0.88	-0.20 $\pm$ 1.21	-0.47 $\pm$ 0.76	4.14	0.01 ^{\$} *
Executive Function						
TMT-B	0.46 $\pm$ 1.41	0.39 $\pm$ 0.72	-0.30 $\pm$ 1.08	-0.42 $\pm$ 0.86 ^b	3.61	0.02 ^{\$} *

Data are presented as mean $\pm$ standard deviation (SD).

^{\$} p values were obtained by one-way analysis of variance (ANOVA) analysis.

[%] p value was obtained by Fisher's exact probability tests.

* significant differences were found in age, perceptual speed and executive function among the four groups.

^{a-b} post hoc tests by Tukey-Kramer analysis further revealed the source of ANOVA difference ($p < 0.05$, a: NC-APOE $\epsilon 4-$ vs. RGD-APOE $\epsilon 4+$; b: NC-APOE $\epsilon 4-$ vs. RGD-APOE $\epsilon 4-$).

Composite scores: Episodic Memory was determined by AVLT-DR and CFT-IR; Working Memory was represented as the DST; Visuospatial Function was obtained by CFT tests; Perceptual Speed was analyzed with the SDMT and the TMT-A; Executive Function was established by TMT-B. Abbreviations: NC, normal control; RGD, remitted geriatric depression; M/F, male/female; AVLT-DR, auditory verbal learning test-delayed recall; CFT-IR, Rey-Osterrieth complex figure test-immediately recall; DST, digit span test; CFT, Rey-Osterrieth complex figure test; SDMT, symbol digit modalities test; TMT, trail-making test.

Table 2

The influences of RGD and APOE ε4 allele on the bilateral HFC networks.

Brain region	BA	Cluster size (mm ³)	Peak MNI coordinate (LPI)			Peak Z score
			X	Y	Z	
Main effects of RGD on the bilateral HFC networks						
Left HFC network						
L middle frontal gyrus	8/9	5454	-21	12	48	-3.43
L medial prefrontal cortex	10	3348	-12	54	18	-3.22
R middle frontal gyrus/superior frontal gyrus	6/8	5184	30	0	54	-3.11
R inferior occipital gyrus/lingual gyrus	17/18	7695	33	-84	-9	4.56
Right HFC network						
L somatomotor area	6	7236	-15	-18	72	-4.00
L middle frontal gyrus	9	2079	-33	12	42	-3.43
R superior parietal lobule	7	4293	30	-63	33	3.38
R posterior middle temporal gyrus	21/22	3240	54	-54	12	3.54
R lingual gyrus	19	6615	21	-69	-6	4.26
R cuneus	18	2349	15	-75	6	3.01
Main effects of APOE ε4 allele on the bilateral HFC networks						
Left HFC network						
B medial prefrontal cortex/anterior cingulate cortex	9/10/32	10665	6	42	27	-3.72
R supramarginal gyrus	22/40	6345	69	-24	21	4.02
L insula	13	6615	-42	3	-3	3.22
R insula	13	6345	39	0	-9	3.34
Right HFC network						
B medial prefrontal cortex/anterior cingulate cortex	9/10/32	11232	-12	42	27	-3.86
R inferior temporal gyrus	37	4023	45	-72	-9	-3.36
L inferior temporal gyrus	20	2349	-42	-3	-36	-3.17
R right inferior frontal gyrus	45	2889	60	18	12	-2.98
L inferior parietal lobule	40	2511	-60	-33	30	3.46
L insula	13	2592	-33	-21	18	3.06
Interactive effects of RGD and APOE ε4 allele on the left HFC network						

Brain region	BA	Cluster size (mm ³)	Peak MNI coordinate (LPI)			Peak Z score
			X	Y	Z	
B dorsal anterior cingulate cortex/medial prefrontal cortex	9/10/32	5562	3	39	21	-3.54
B somatomotor area	6/4	2754	24	-24	72	3.40
R inferior occipital gyrus	18/19	2376	30	-84	-9	3.69

Abbreviations: RGD, remitted geriatric depression; APOE, Apolipoprotein E; HFC, hippocampal functional connectivity; MNI, Montreal Neurological Institute space; BA, Brodmann's area; B, bilateral; R, right; L, left.