Neural Basis of the Association between Remitted Geriatric Depression and APOE ε4 Allele in the nondemented elderly

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Introduction: Geriatric depression (GD) and apolipoprotein E (APOE) ε4 allele have been recognized as the risk factors of Alzheimer's disease (AD).[1-2] Coexistence of previous depressive episodes and APOE ε4 allele could cause significant persistent cognitive impairment in the nondemented elderly.[3] However, neural basis of the association between the two factors remains unclear. In AD-spectrum disease and depressive episodes, the hippocampus, the key region in regulating high-order cognitive function, has been impaired.[4-5]The purpose of this study was to detect the influence of remitted geriatric depression (RGD) and APOE ε4 allele with their interaction on hippocampal functional connectivity (HFC) networks.

Methods: Thirty-one RGD （Mean ages: 67.88±4.48 y）and 29 normal control (NC, Mean ages: 70.83±3.86 y) subjects were recruited and further divided into four subgroups according to their APOE genotypes（for NC group: 7 APOE4+ and 22 APOE4- subjects; for RGD group: 11 APOE4+ and 20 APOE4- subjects）. Each subject completed neuropsychological tests and underwent MRI EPI scans (General Electric 1.5T). Seed-based network analysis was employed and 2×2 factorial analysis of variance was used to test the main effects and interactive effects of RGD and APOE ε4 allele on HFC networks. The mean Z-values of the resulting clusters were extracted to detect the altered pattern among groups. Additionally, multivariate regression analysis was used to identify the behavioral significance of these altered HFC networks.

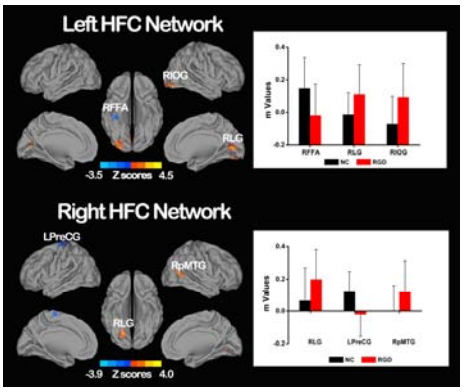

Figure 1. Main effects of RGD on HFC bilateral networks.

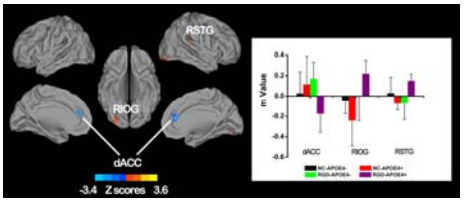

Figure 3. Interactive effects of RGD and APOE ε4 allele on the left HFC Network.

Results: 1. As shown in **Figure 1**, the main effect of RGD on the bilateral HFC networks was mainly located in the parietal-occipital regions. Specifically, in the left HFC network, RGD patients showed decreased HFC in the right fusiform area (FFA) and increased HFC in the right lingual gyrus (LG) and inferior occipital gyrus (IOG) compared to NC group; while for the right HFC network, RGD patients showed decreased HFC in the left precentral gyrus and increased HFC in the right posterior middle temporal gyrus and LG.

2. Main effects of the APOE ε4 allele were mainly in bilateral insula and regions within default mode network, as shown in **Figure 2**. Particularly, APOE ε4 allele carriers showed increased HFC in the right middle temporal gyrus, right insula and left insula/superior temporal gyrus (STG) and decreased HFC in the left parahippocampal gyrus and bilateral dorsal medial prefrontal cortex /anterior cingulate cortex (ACC) compared with APOE ε4 noncarriers. While for the right HFC network, several regions demonstrated decreased HFC for APOE ε4 carriers, including the right FFA, left retrospelenail cortex, left dorsal lateral prefrontal cortex and left medial prefrontal cortex except for left caudate showing increased HFC in APOE ε4 allele carriers.

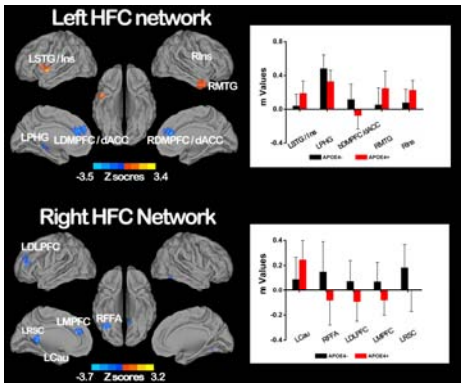

Figure 2. Main effects of APOE ε4 allele on HFC Networks.

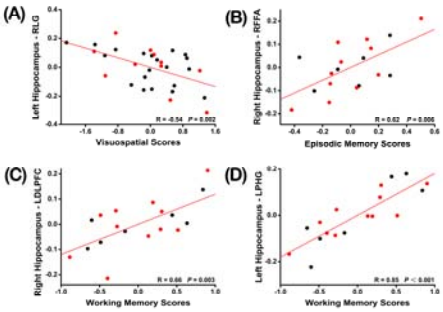

Figure 4. Behavioral significance of abnormal HFC networks in RGD patients (A) and APOE ε4 allele carriers (B), (C), (D)

3. As described in **Figure 3**, the interactive effects of RGD and APOE ε4 allele were found in three regions including right IOG, right STG and the bilateral dorsal ACC (dACC) that connected to left hippocampus. Specifically, RGD patients with APOE ε4 allele showed significantly decreased HFC in dACC and right IOG and increased HFC in right STG.

4. For RGD patients, the increased left HFC network in the right LG was negatively correlated with visuospatial scores. On the other hand, for APOE ε4 allele carriers, the decreased left HFC in the left PHG, as well as decreased right HFC in the left DLPFC, are positively correlated with working memory scores, while the decreased right hippocampus connectivity to right FFA is positively correlated with episodic memory scores, as shown in **Figure 4**.

Discussion and Conclusion: In this study, we first confirmed the factors of RGD and APOE ε4 allele could affect HFC network distinctively, the altered pattern of which could be supported by previous studies[6-7] More importantly, we further demonstrated that the two factors could exert interactive effects on the left HFC network, especially for dACC, the key region of the interaction between cognitive and emotional processing, was significantly disrupted. Several studies have indicated the persistent impairment of dACC in RGD with its relation to cognitive decline, as well as its role played in the conversion to AD for APOE ε4 allele carriers in AD-spectrum.[8-9] Therefore, we suggest that such disconnection may imply cognitive deterioration, even the conversion to AD for RGD patients with APOEε4 allele over time. Conclusively, our findings indicated the neural substrate of the association between RGD and APOE ε4 allele, which may contribute to monitor the cognitive decline as well as it conversion to AD in high-risk group.

Reference: 1. Byers AL, et al. Nat Rev Neurol. 2011; 7, 323-331; 2. Corder EH, et al. Science. 1993; 261, 921-923; 3. Corsentino EA, et al. Am J Geriatr Psychiatry. 2009; 17, 155-165; 4. Bai F, et al. Neurosci Lett. 2009; 450, 85-89; 5. Steffens DC, et al. Am J Geriatr Psychiatry. 2011; 19, 4-12; 6. Veer IM, et al. Front Syst Neurosci. 2010; 4, pii: 41; 7. Sheline YI, et al. J Neurosci. 2011; 30, 17035-17040; 8. Wang L, et al. Am J Geriatr Psychiatry. 2012; 20, 653-663; 9. Mosconi L, et al. Neurology. 2004; 63, 2332-2340.

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