Imaging the Functional Pathology in ApoE 4 Carriers by the Hippocampus Functional Connectivity

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Introduction: The allele 4 of apolipoprotein E (ApoE4) is an established susceptibility gene for late onset Alzheimer's disease (AD). Research on the risk factor of AD in the human and animal models has highlighted the important contribution of ApoE4[1,2]. Despite the extensive work dedicated to investigating the basic neurobiological mechanism of ApoE4 genotype as related to developing AD risk in younger and older populations, little is known about whether and how the ApoE4 genotype affects the functional brain network in middle-aged, cognitively healthy populations of ApoE4 carriers. In the present study, we test the hypothesis that the resting-state functional connectivity between the hippocampus and the rest of the brain regions is reduced among the middle-aged, cognitively healthy APOE4 carriers compared to that of nonAPOE4 carriers.

Methods: A total of 46 neurologically healthy 44- to 65-year-old study subjects participated in this study. APOE genotype characterization results showed that 20 study subjects carried APOE4 (4 subjects had the ε4/ε4 genotype, 16 subjects had the ε3/ε4 genotype) and 26 subjects did not carry APOE4 (2 subjects had the ε2/ε3 genotype, 24 subjects had the ε3/ε3 genotype). The two groups of APOE4 carriers and nonAPOE4 carriers matched well in age, education levels, and neuropsychological performances. All study participants received fMRI scans at a GE 3T scanner. Imaging datasets included whole-brain anatomical dataset and a 6-min resting-state BOLD-fMRI dataset. Functional connectivity between the hippocampus and the rest of brain region was obtained for each study subject using cross-correlation of the spontaneous low-frequency fluctuations in the resting-state dataset. Group analysis was then performed using a student *t*-test to determine the difference in the hippocampal functional connectivity (HFC) between the groups of APOE4 carriers and nonAPOE4 carriers.

Results: Compared to nonAPOE4 carriers, the strength (area) of HFC in the APOE4 carriers was reduced, especially in the left dorsal lateral prefrontal cortex (DLPFC), bilateral posterior cingulate cortex (PCC) and middle temporal gyrus (MTG), as shown in Figs. 1A and 1B. A group *t*-test demonstrated that the significantly reduced HFC regions presented primarily in the subcortical regions, including the bilateral caudate, putamen, thalamus, etc. The HFC regions were increased in the paracentral lobule ($p< 0.05$), as shown in Fig. 1C.

Discussion: Previous studies have identified the ApoE4 gene as having a strong impact on the neuropathological basis of neurodegeneration in general and AD in particular [2, 3]. In the present study, we demonstrated that the strength of HFC at resting-state in middle-aged, cognitively healthy APOE4 carriers is reduced, and that the altered patterns of HFC are associated with ApoE4 genotype. It is noteworthy that the brain regions with significantly reduced HFC were in the striatum and thalamus; this is consistent with recent findings that abnormal amyloid, detected with 11C-PiB PET, is deposited in the striatum and thalamus [3], especially in ApoE4 carriers. It is hypothesized that the reduced HFC may reflect the abnormal amyloid deposit. This increased amyloid is associated with cerebral amyloid angiopathy (CAA), which is frequently exhibited in AD patients [4]. Human and animal models have demonstrated CAA and CAA-related capillary occlusion in striatum and thalamic vessels [5]. Therefore, the observed HFC reduction may indicate the risk of capillary CAA that could result in occlusion, cerebral blood flow disturbances, and lacunar infarction, thus, providing an additional risk mechanism for ApoE4 in AD.

Conclusion: The present results have shown that the alteration of the HFC pattern is significantly associated with the ApoE 4 genotype and that the alteration of the HFC pattern in ApoE 4 carriers could serve as a surrogate biomarker for the risk of AD.

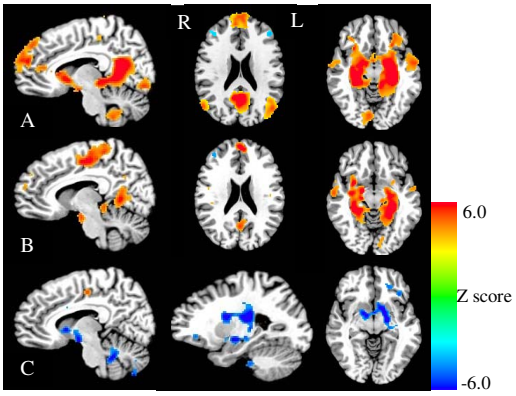

Fig. 1. **A.** fcmap of HFC for ApoE4 noncarrier group (one-sample *t*-test, $p< 0.001$, corrected with cluster size 368 mm^3); **B.** for ApoE4 carrier group (one-sample t-test, $p< 0.001$, corrected with cluster size 368 mm^3). The HFC activity (area) for ApoE4 carriers group was decreased in the regions of the bilateral MTG and PCC, and prefrontal cortex system (bilateral medial frontal cortex and DLPFC). **C.** Difference map in HFC between these two groups. Significantly reduced HFC activity was evident in the subcortical regions, including the bilateral caudate, putamen, thalamus, etc. (two-sample *t*-test, $p< 0.05$, corrected with cluster size 4048 mm^3).

References

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