Opposite neural trajectories of Apolipoprotein E ε4 and ε2 alleles with aging associate with different risks of Alzheimer's disease

Hao Shu1,2, Yongmei Shi1, Gang Chen1, Zan Wang1, Duan Liu1, Chunxian Yue1, B. Douglas Ward2, Wenjun Li2, Zhan Xu2, Guangyu Chen2, Qihao Guo1, Jun Xu1, Shi-Jiang Li2, and Zhijun Zhang1

1Neurologic Department of Affiliated ZhongDa Hospital, Neuropsychiatric Institute and Medical School of Southeast University, Nanjing, Jiangsu, China, 2Department of Biophysics, Medical College of Wisconsin, Milwaukee, Wisconsin, United States

Purpose: The altered brain functions detected by neuroimaging methods in cognitively normal APOE ε2 carriers have been linked to insidious AD development. However, recent studies have demonstrated the APOE ε2 allele has altered brain functions as in the case of the APOE ε4 allele, despite their opposite susceptibilities to AD1-2. Given aging is another established risk factor of AD, we hypothesize that aging could differently influence the effects of the APOE ε2 and ε4 alleles that contribute to their different AD risks.

Methods: A total of 129 cognitively normal elderly, including 36 ε2 carriers, 44 ε3 homozygotes and 49 ε4 carriers, were recruited and underwent resting-state functional MRI scans (Simens Verio 3.0T scanner). Individual posterior cingulate cortex functional connectivity (FC) network were established to represent the pattern of default mode network (DMN). Difference of DMN FC among groups with its cognitive significance was detected. Stepwise regression analysis was applied to examine how the altered DMN FC strengths are differently affected by aging and the years of education among the three APOE alleles.

Results: We observed the reduction of DMN FC occurred in both APOE ε2 and ε4 carriers compared with ε3 homozygotes (Figure 1A and Figure 2A). Behavioral, the altered DMN FC positively correlated with information processing speed in both ε2 and ε4 carriers. Such a relationship was not found in ε3 homozygotes (Figure 1C and 2C).

Further post hoc stepwise regression analysis with inclusion of the interactions between APOE status and education years revealed that the extent to which the effect of education years on the DMN FC values is different by APOE polymorphism, in addition to the effects of APOE genotype and age. Relative to APOE ε3 homozygotes, APOE ε4 carriers showed a significant increased slope (β=0.002, p<0.0001), whereas ε2 carriers showed a decreased slope (β=-0.002, p=0.02).

Discussion and Conclusion: In this study, our major new finding is that APOE ε2 and ε4 carriers have opposite trajectories of FC changes with aging in the DMN, primarily in the bilateral ACC regions, although both APOE ε2 and ε4 carriers showed similar decreased FC compared with ε3 homozygotes. These findings revised the previous conceptual framework of the neuroimaging characteristic of APOE polymorphism that the aging trajectories in brain function influence the susceptibilities to AD for different APOE alleles, in addition to their antagonistic pleiotropic effects of both APOE ε2 and ε4 carriers on the neural network activity in an opposite way to link their different risks for late AD onset3-4. Further, we proposed that age should be included as an important regulator when investigating the role of APOE polymorphism in the development of AD at neural system level.