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

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Target audience Researchers studied on translational medicine in neuroimaging and neurodegenerative disease.

Purpose Apolipoprotein E (APOE) ε4 allele is the confirmed genetic risk factor and APOE ε2 allele is the protective factor for Alzheimer's disease (AD). The altered brain functions detected by neuroimaging methods in cognitively normal APOE ε4 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 AD[1-2]. 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 **1B, Figure 2A** and **2B**). Behaviorally, 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 (**Figrue 1C** and **2C**).

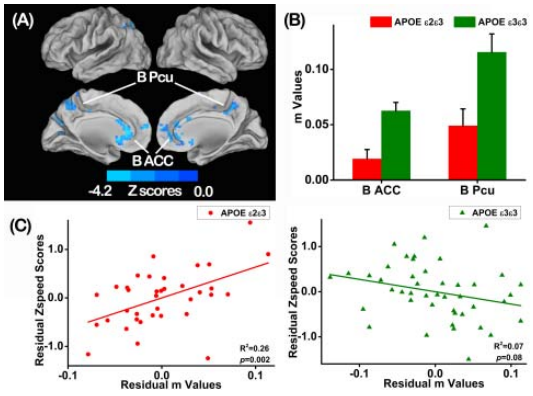

Figure 1 Decreased DMN FC in APOE ε2 carriers with its significance in information processing speed.

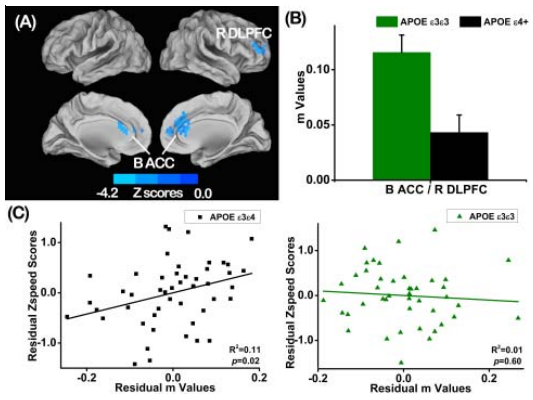

Figure 2 Decreased DMN FC in APOE ε4 carriers with its significance in information processing speed.

Bilateral ACC region showing decreased DMN FC in both APOE ε2 and ε4 carriers compared with ε3 homozygotes was identified (**Figure 3A** and **3B**). With the stepwise regression analysis regarding ε3 homozygotes as the reference group, the model with APOEε2, APOEε4, APOEε2 × age interaction, APOEε4 × age interaction and education years provided the best prediction to the DMN FC value in this region (adjusted R^2=0.185, p<0.0001). Specifically, APOE ε2 and ε4 carriers have opposite trajectories of FC changes with aging. Along with aging, ε2 carriers showed increased FC, while ε4 carriers exhibited decreased FC.

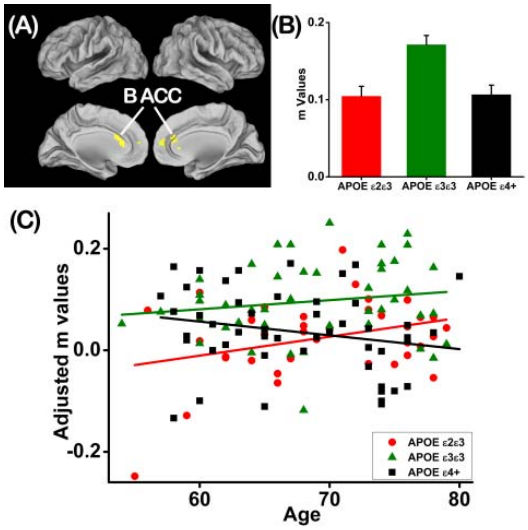

Figure 3 Opposite trajectories of DMN FC with aging between APOE ε2 and ε4 carriers.

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=0.001), whereas ε2 carriers showed a decreased slope (β=-0.002, p=0.02).

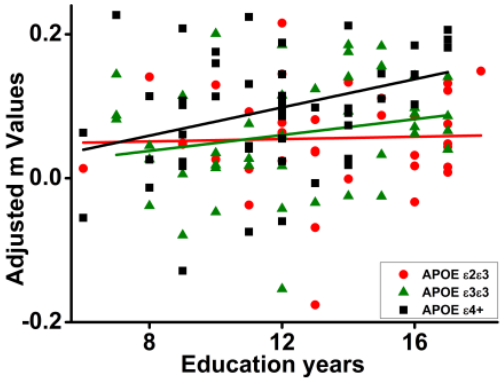

Figure 4 Discrepant functional trajectories with education years among the three APOE alleles.

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 directly effects on brain activity. Our data support the 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 onset[3-4]. 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.

References 1. Trachtenberg AJ et al. Neurobiol Aging 33: 618 e611-618 e613; 2. Trachtenberg AJ et al. NeuroImage 59: 565-572. 3. Han SD et al. Alzheimer's & dementia 4: 251-254. 4. Morris JC, et al. Ann Neurol 67: 122-131.