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·Letter to the Editor·

Apolipoprotein E gene polymorphisms associated with processing speed and executive functions in healthy Han Chinese

Dear Editor,

A few studies have focused on exploring *APOE* gene-related effects on cognitive functions and brain activities in healthy populations. Bondi *et al.* found that ε4 carriers perform significantly worse on the California Verbal Learning Test than non-carriers in non-demented old subjects (mean age, 72 years)[1]. But the results are not entirely consistent. For example, Scarmeas *et al.* found no effect of the ε4 allele on neuropsychological performance[2] in young adults, and Jochemsen *et al.* found that the ε4 allele is associated with age-related cognitive decline[3]. Furthermore, protective and negative effects of the ε2 allele on cognition are inconsistent[4, 5]. APOE ε2 is thought to be a protective allele for AD in the elderly population due to its role in the superior cognitive performance of ε2 carriers compared to ε3 or ε4 carriers[5]. However, the ε2 allele has also been found to have a negative effect on AD pathology[4].

In order to test whether the ε4 and ε2 alleles of *APOE* affect processing speed and executive function in a healthy population, and whether there are age-specific effects, we selected 425 healthy Han Chinese aged 16 to 70 years and gave them several cognitive tests: the Stroop color and color-word interference, trail-making (A and B), logical memory, and visual reproduction tests. All participants were genotyped for two single-nucleotide polymorphisms (SNPs; rs429358 and rs7412) contributing to the *APOE* ε2, ε3, and ε4 alleles. We analyzed the association between *APOE* genotypes and attention, memory, and executive functions using analysis of covariance (ANCOVA) in participants with and without age-stratification.

We found that *APOE* genotypic status significantly affected the completion time to read the color of words (StroTi) in a Stroop color test (F = 3.45, df = 2, P = 0.033) in the total samples. *Post-hoc* ANCOVA revealed that participants with *APOE* ε4/- (i.e., ε4/ε4 and ε3/ε4) showed inferior performance in the StroTi test compared to those with *APOE* ε3/ε3 (P = 0.009). Furthermore, we performed analysis in two age groups (16–39 years and 40–70 years) and found a significant difference in the young group only (ANCOVA: F = 3.728, P = 0.025; *post-hoc* ANCOVA: P = 0.008) (Fig. 1A, Supplementary Material Tables S1 and S2). Also, participants aged 40 to 70 years showed significant *APOE* genotypic effects on completion time in the trail-making-A test (F = 3.47, P = 0.034; Tables S1 and S2). *Post-hoc* ANCOVA tests revealed that *APOE*ε2/- (i.e., ε2/ε2 and ε2/ε3) participants spent more time completing the trail-making-A test compared to those with *APOE*ε3/ε3 (P = 0.015) or ε4/- (P = 0.025) (Fig. 1B). However, no difference remained significant after Bonferroni correction.

These findings suggested that the *APOE* ε4 allele affects executive functions and the ε2 allele affects attention in different age groups, although the effect sizes are small. This is partly consistent with previous findings that performance in neuropsychological tests, particularly those involving processing speed, executive function, and memory, is impaired in AD patients and/or normal ε4 allele carriers[6]. We found that the ε4 allele was associated with impaired performance in the StroTi test, a complex task assessing cognitive processes including cognitive plasticity, attention, and executive functions. This effect was stronger in the younger group, aged 16 to 39 years old, in particular. Although previous studies have demonstrated that the *APOE* ε4 allele has negative effects in elderly people with regard to cognition and neuronal activity[7], actually increasing numbers of studies have found that this effect occurs even when the participants are <40 years old[6]. The mechanism by which *APOE* variants impair executive functions is probably due to the effect of Aβ[6]. Ohm *et al.* suggested that histopathological features may precede the onset of AD by up to 50 years[8]. Han *et al.*[9] suggested that ε4 allele has an effect of antagonistic pleiotropy. Another view is that ε4 may have a negative impact on cognition or neuronal activity in young or middle-aged population[6, 10]. For example, Ghebremedhin *et al.* showed that

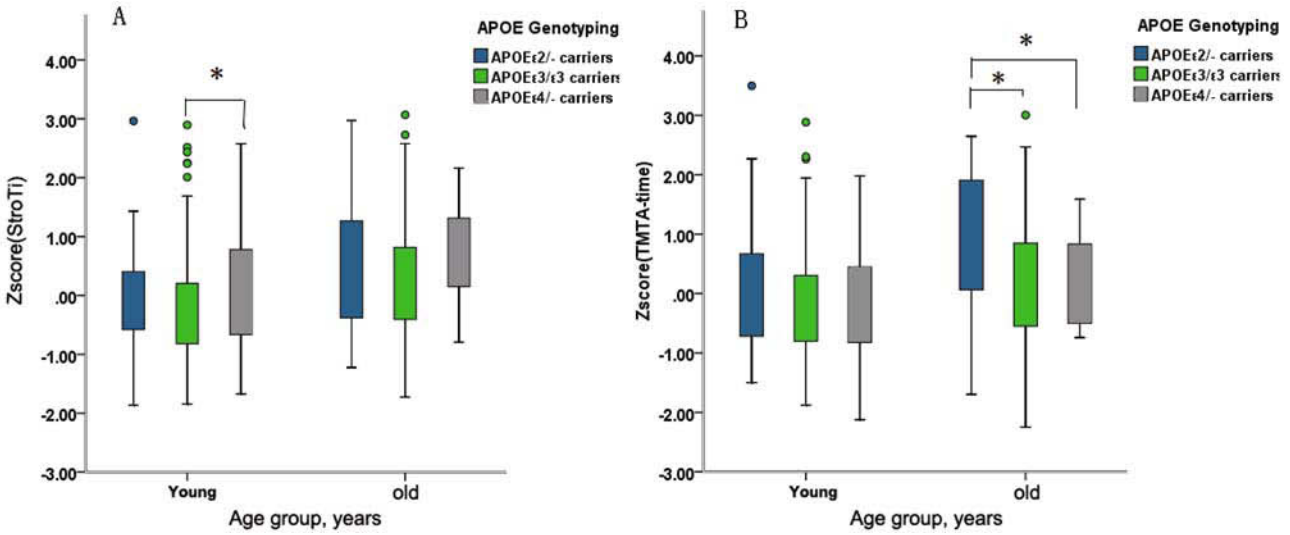

Fig. 1. Comparison of standardized residuals of Stroop color (StroTi) (A) and trail-making-A (TMT-A) (B) tests in young and old groups. APOEε2/- includes ε2/ε2 and ε2/ε3; APOEε4/- includes ε3/ε4 and ε4/ε4. StroTi, completion time of reading the color in Stroop color and color-word interference tests. TMTA-time, completion time of trail-making, part A. Young group: 16–39 years. Old group: 40–70 years. ****P* **<0.05.

cognitive deficits caused by neurofibrillary tangles are more frequently seen in ε4 carriers than in non-ε4 control group between 22 and 46 years[10].

We found that *APOE* ε4 did not have a similar effect on executive functioning in the older group, and this does not support the findings from previous studies. One possible reason is that *APOE* ε4 has selective effects at different ages. A meta-analysis showed that increasing age is associated with smaller group differences between the *APOE* ε4 and non-*APOE* ε4 groups[11]. The second reason may be that the elderly were still in the early post-amyloid stage, and their declining cognitive functions were concealed by compensatory increases in brain activation, albeit followed by ultimate decline. In addition, the lack of significant differences may be due to the insufficient sample size for the 40–70 year-old group.

Furthermore, we found that the *APOE* ε2 allele was associated with impaired performance on the trail-making-A test, a complex problem-solving task mainly reflecting processing speed and mental flexibility in the elderly only. Previous studies have provided evidence that *APOE* ε2 carriers perform better than *APOE* ε3 or ε4 carriers, probably because the *APOE* ε2 allele binds more efficiently to the microtubule-associated protein tau than the ε4 allele. However, studies found that the *APOE* ε2 allele is a risk factor for AD[4], which suggests that *APOE* ε2 has negative effects on cognition similar to ε4 in the elderly. A possible mechanism may be the increased plaque pathology in individuals with APOE ε2[4] or APOE ε2 protein in disequilibrium, accelerating the pathological process of AD, initiating synaptic dysfunction and leading to cognitive decline[12]. We assume that elderly *APOE* ε2/- individuals are likely to show worse attention and processing speed than younger individuals due to neuropathology[4] or brain activity dysfunction[13].

Several issues should be addressed to understand the current findings. In order to capture important age-related information exhaustively in the preliminary study[14], our findings and discussion are mainly based on the results without multiple comparison correction. The multiple comparison correction is important as it reduces the probability of false-positives (type one errors) although it may increase the probability of false-negatives if the variables are not independent[15]. In conclusion, the current findings provide further evidence to support the hypothesis that the APOE gene affects processing speed and executive function in the normal population, with age-specific effects.

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