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The effects of two Alzheimer's related genes APOE and MAPT in healthy young adults: An attentional blink study

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Abstract

Background genetic risk factors start to affect the brain and behavior in Alzheimer's Disease (AD) before clinical symptoms occur. Although AD is mainly associated with memory deficits, attention and executive dysfunctions can present at the early presymptomatic stages in middle age for those with non-modifiable risks. Here, we investigated whether known risk genes for AD already affected attention in young adulthood.

Methods a total of 392 healthy young adults aged around 20 years underwent genetic testing for risks of dementia (APOE and MAPT) and performed a computerized cognitive test for temporal attention called the Attentional Blink (AB) task, in which patients with dementia tested in previous studies often showed reduced performance. Here, the AB task was analyzed using repeated-measurements analysis of variance for the ability of visual perception, attention deployment and temporal memory encoding/binding performance.

Results the results showed that all participants exhibited AB effects. Importantly, genetic risk factors had statistically significant influence on temporal attention depending on sex in healthy young adults. APOE4 status was associated with enhanced attention deployment in males ($F(1, 124) = 8.285$, $P = .005$, $\eta^2 = .063$) but not females, while MAPT AA carriers had poorer performance in AB but only in females ($F(1, 254) = 4.114$, $P = .044$, $\eta^2 = .016$). No genetic effects were found for visual perception and temporal memory binding errors between high and low risk groups.

Conclusions We provided evidence that both APOE and MAPT start to affect attentional function as early as young adulthood. Furthermore, unlike previous findings in older people, these genes had a differential effect for males and females in young adults.

Key words: Alzheimer's disease, attentional blink, APOE, MAPT, dementia, genetic risk factors

Introduction

Alzheimer's disease (*AD*) is an age-related neurodegenerative disease that is accompanied by cognitive impairments such as memory loss, impairments of learning, and impairments in executive function in the early stage [1], progressing to speech difficulties, and losing reading and writing skills in the latter stage [2]. As family history of AD increases the likelihood of developing the condition, it is believed that genetic risk factors are key drivers of AD [3]. The main genetic risk factors of AD include Apolipoprotein E (*APOE*)-ε4 allele [3-6], Microtubule-associated protein tau (*MAPT*) [6-9], and other genetic loci discovered in GWAS studies [10]. Previous research on these genetic risk factors showed that people carrying risk genes were more likely to develop dementia in later life and have shown differences in cognitive performance before clinical symptoms occur and in middle and young age [11], so it is important to study how early the effects of these Alzheimer's related genetic risk factors begin in cognitively healthy young adults.

APOE is a protein, which functions to transport lipid and cholesterol [12]. Among its three major alleles (ε2, ε3, and ε4), both homozygotes (ε4/4) carriers and heterozygous carriers (ε4/-) of ε4 are regarded to have a higher risk and earlier onset of AD than noncarriers [13]. The mechanism underlying this association remains unclear, but evidence shows that it may be because APOE ε4 carriers (denoted as APOE4) have an impaired capability to remove amyloid beta (Aβ), a pathological hallmark of AD in the brain among other neuropathological mechanisms [12].

As another genetic risk factor of AD, the MAPT gene encodes the tau protein, a protein that is associated with stabilizing and assembling microtubules. Containing hyperphosphorylated tau protein, neurofibrillary tangles (NFTs) within neurons are regarded as another hallmark of AD besides Aβ [14]. MAPT has two haplotypes (H1 and H2) [15], and the H1c sub-haplotype [16]. Several single nucleotide polymorphisms (SNP) contained in H1 haplotype, such as rs242557 AA genotypes, are considered to increase the risk of AD

[17].

Previous studies have found that these two genetic risk factors are linked with worse cognitive functioning in healthy older individuals. APOE ε4 allele was associated with poorer executive function [18], an increased risk of mild cognitive impairment [19] and faster cognitive decline [19-22] in older people. Interestingly, in younger healthy individuals, some emerging research has found cognitive advantage associated with episodic memory [23], verbal fluency [24], learning [25], and attention [4] in young APOE4 carriers. In this respect, an "antagonistic pleiotropy" hypothesis was proposed to explain the apparent "beneficial" effect of APOE4 on cognition in early life and the detrimental effect in later life [26]. However, such advantage of APOE4 on cognition in early life was not found in some other studies [27-30]. This inconsistency may result from the different tasks used in these studies suggesting that the effects of APOE4 in early adulthood may vary among different cognitive domains and APOE also interacts with other genetic and environmental factors. So, as discussed later, in our study, we have chosen a robust psychophysics task that can be sensitive to subtle effects of genes.

Less studied than APOE, the relationship between MAPT and cognitive performance is also mixed. In an experiment carried out in 350 adults with progressive supranuclear palsy (PSP), the rs242557 A carriers performed better than noncarriers in general cognitive function, executive function, and attention [31]; other research found that H1 homozygosity carriers performed worse in a picture memory task than H2 carriers [32], but a study on 1191 patients with Parkinson's Disease (PD) found no association between H1 haplotype and the psychometric results [33]. How MAPT relates to cognition in middle age and young adults remains understudied.

Although the effects of Alzheimer's related genetics risk factors such as APOE and MAPT are extensively studied in older patients and controls, their effects on cognitive functioning in younger healthy individuals remains unclear. Also, although memory loss was regarded as the earliest cognitive impairment in AD, and attention and executive dysfunctions being associated with other subtypes of dementia such as dementia with Lewy bodies (DLB), evidence has shown that attention deficits were also an early problem in AD [34, 35]. Some also argued that early memory issues in patients with AD could also be due to poorer attention [36]. Now, it is widely recognized that neuropathology and brain structural and functional changes begin decades before clinical symptoms of AD occur [37]. Early-stage AD provides the best window of opportunity for intervention. However, how genetic risk factors of AD affect key cognitive domains such as attention and executive functions in healthy middle-age or young individuals remain inconclusive. The current study is an extension of the PREVENT-dementia project [38] aimed at establishing a cross lifespan knowledge base for genetic and environmental risk factors of dementia. Previously, we have shown in the same cohort that young APOE4 and MAPT AA carriers have reduced functional connectivity in the default mode network and thinner cortex in areas (temporal and frontal cortices) that typically develop AD pathology including tau [39, 40]. Although research in the field including our own studies have uncovered striking changes in brain cortical morphology and functional connectivity as early as young adulthood and middle-age, sensitive measures of early cognitive changes due to genetic risks of AD is still lacking.

Hence, in the present study, we aimed to explore the effects of genetic variants (APOE and MAPT rs242557) in young healthy individuals performing a well-established task called the attentional blink (AB) task [41]. In the AB task, people are asked to detect two targets among a series of distractors in a rapid serial visual presentation (RSVP) stream. In general, people show a deficit in reporting the second target if it appears within 100-500ms after the first target [41]. One theoretical explanation for the AB deficit is the competition of attentional resources between two targets [42], and this task was used to test people’s ability to allocate attention and temporally integrate episodic information in temporal processing [43]. In addition, the AB task has been used to detect the cognitive deficit of patients suffering from neurodegenerative diseases. In a previous study, people with PD showed a different pattern of errors from healthy counterparts in the AB task [44]. It is also shown that AB performance was significantly impaired in both AD and DLB although patients with DLB had a more extended and severer reduction in performance than AD, i.e., deeper and longer blinks [45]. However, it is unknown whether healthy young people with genetic risk factors of AD can also show a different performance in AB even, as previous studies may suggest, a 'beneficial' effect of these risk factors in younger people.

As discussed previously, existing evidence is inconsistent about whether and how genetic risks impact attention in neurodegenerative conditions in young adulthood, although popular views such as the so called 'the associated antagonistic pleiotropy hypothesis exist [46]. The mixed findings in the literature were partly due to different cognitive tests used in these studies because traditional pen and paper based clinical tools are unlikely to be sensitive to young healthy individuals due to 'ceiling effects', and computerized cognitive tests also suffer from many limiting factors such as biases caused by cognitive strategy, level of education, confounding sensory perception functions, cultural and other methodological variations. The attentional blink task chosen here however offers an ideal paradigm to examine cognitive functioning in young people because it is a challenging and robust test that is minimally affected by mental strategy, practice effects, linguistic knowledge and can be easily automated on computers [41]. Previous studies have shown a profound impairment in the AB and rapid visual tests across multiple dementia subtypes [45], as well as several developmental disorders in young people [47, 48].

According to the results from previous studies, we hypothesized that APOE4 carriers would have a reduced AB deficit than noncarriers, and for the MAPT (rs242557), people with AA genotypes (the high-risk variant) would have an increased AB deficit than those with G genotype.

Method

Participants

From Chinese students studying undergraduate degrees at the Southwest university in Chongqing, participants from both sexes were recruited using online and offline advertisements on campus. People with severe neurological and psychiatric conditions were excluded. We also excluded anyone majoring in sports, arts, or music because these subjects have a different university entrance requirements from other subjects. The above inclusion / exclusion criteria enhanced the cognitive homogeneity of the participants due to the selection processes and the standard entrance requirements of the university. All participants have given written informed consent and received compensation for their participation. This study was approved by the Ethic Committee of Psychological Research at Southwest University.

Procedure

The attentional blink task was implemented in E-Prime 2.0. A typical trial in the AB task is shown in Figure. 1. In each trial, the participant firstly pressed any key on the keyboard to start the trial. They then saw a blank (grey) screen for 200 ms followed by a series of letters at the centre of the screen presented in random order. Among the stream of letters (A, B, C, D, F, H, J, K, L, N, P, R, T, V, X, Y), there were two one-digit numbers (2, 3, 4, 5, 6, 7, 8, 9) positioned pseudo randomly in the RSVP stream. Each letter or digit appeared on the screen for only 50 ms, and the inter-stimulus interval was set to zero. Thus, the stimulus onset asynchrony (SOA) was 50 ms. In each trial, there were 27 letters as distractors and 2 one-digit numbers as targets (represented as Target 1 and Target 2 or T1 and T2 for short). At the end of the trial, the participant was asked to respond by typing in the identities of the two target numbers, in the order they saw them, and to ignore the distractors (letters). To avoid visual confusion about the physical forms of the stimuli that are not related to attentional processing, one-digit numbers resembling letters (e.g., 0, 1) and letters resembling numbers (e.g., I, O, Q and S) were not used.

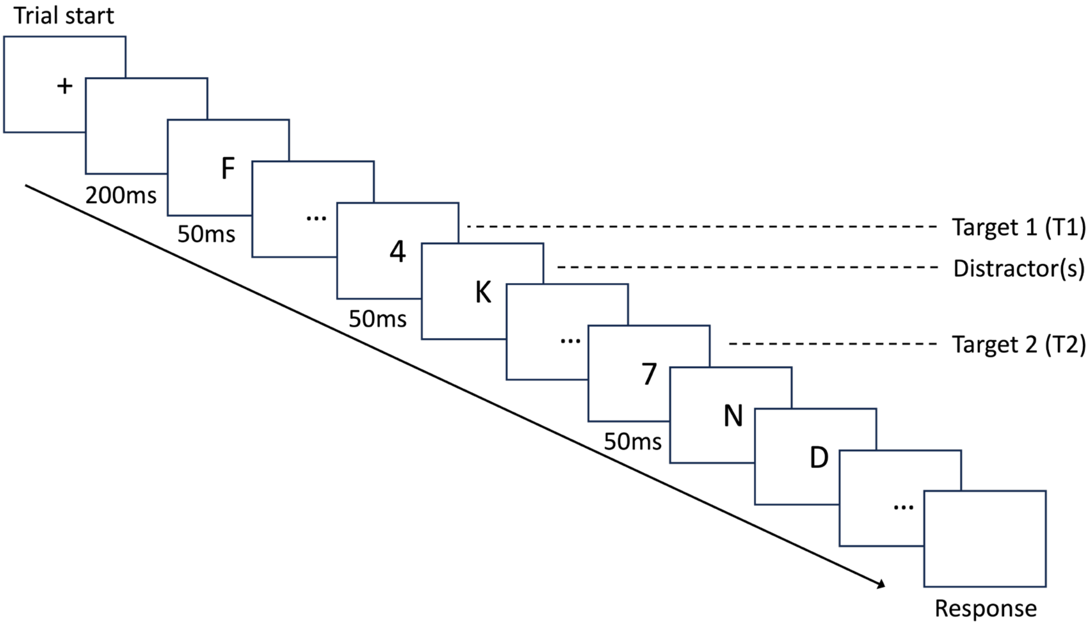

Figure. 1 A schematic diagram of a typical trial. Each letter and number were presented for 50 milliseconds, with no inter-stimulus interval. T1 appeared at the 6th to 12th positions from the beginning of the trial. T2 was positioned after T1 at 1, 2, 3, 4, 5, 6, 8, 10, or 12 lags. Lag 1 means no intervening distractor between T1 and T2; lag 2 means 1 intervening distractor between T1 and T2; and so on.

T1 appeared randomly at the 6th to 12th positions from the beginning of the stream. T2 was positioned after T1 by 1, 2, 3, 4, 5, 6, 8, 10, or 12 positions (i.e., the lag between T1 and T2 was 1, 2, 3..., or 12). Combining the different positions of T1 and T2, there were a total of 63 trial types. The computer presented the 63 trial types twice (two cycles) giving 126 trials. Within each cycle, the 63 trials were randomized for each participant. After finishing 50 trials, participants had a break of proximately one minute.

Before the start of the actual experiment, the participants received instruction and two practice runs, each of which contained four trials. In the first practice run, a trial was the same as the trial in the actual experiment in all but the following aspects. Each letter or number appeared for a longer duration of 500 ms. Participants were informed that the speed of presentation was slowed down during practice. After each participant's response, feedback of correct (√) or incorrect (×) was provided on the screen. If the participant could not correctly respond to all 4 trials, they had to repeat the instruction and the first practice run. After the first practice run, a second practice run was conducted, but this time, the stimulus duration was the same as the actual experiment.

Genotyping

This study investigated APOE and MAPT rs242557, and the former was determined by rs7412 and rs42935. The genotypes were performed by a Mass Array system (Agena iPLEX assay, San Diego, United States). Approximately 10-20ng of genomic DNA was isolated from saliva samples. The sample DNA was amplified by a multiplex Polymerase Chain Reaction (PCR), then the obtained products were used for locus-specific single-base extension reaction. Finally, the resulting products were desalted and transferred to a 384-element SpectroCHIP array. The alleles were discriminated by mass spectrometry (Agena, San Diego, United States).

For rs7412 the PCR primers were ACGTTGGATGGCCCCGGCCTGGTACACTG and ACGTTGGATGACCTGCGCAAGCTGCGTAAG; the unextended primer was CCGCTGCCGATGACCTGCAGAAG. For rs429358, the PCR primers were ACGTTGGATGTCGCCGCGGTACTGCACCA and ACGTTGGATGCTGTCCAAGGAGCTGCAGG; the unextended primer was GACATGGAGGACGTG. For rs242557, the PCR primers were

ACGTTGGATGAGACCCTGTGAGATCATCCC and ACGTTGGATGTACAAAGCAGTTGGCTTCGC; the unextended primer was CCATCAGTTGGCTTCGCCCAGGGT.

Based on genotypes of rs7412 and rs429358, carriers of ε4/ε4 or ε4/ε3 were combined into a single APOE4 group. Given that AA was the high-risk genotype at MAPT rs242557, we have categorized rs242557 into AA or G carriers in the subsequent analyses. We have also applied Hardy-Weinberg equilibrium tests for each gene in our sample population.

Statistical methods

Outcome measures used in the current study included 1) T1 accuracy – the probability of detecting T1 primarily reflects perceptual functioning; 2) temporal attentional deployment – a conditional probability of detecting T2 given T1 was detected correctly. So, the performance of temporal attention was calculated as a conditional probability of P(T2|T1); 3) AB index - the magnitude of the AB effect (named as AB index here) by calculating the differences between P(T2|T1) measured at lag 4 (where the performance is lowest when SOA is 50ms) and at lag 12 (where the blink has generally recovered). The AB index is a more sensitive way to measure AB effects, and please note that a larger AB index represent a poorer AB performance; and 4) the swap ratio – reporting both targets identities correctly but in the incorrect order. This represents a deficit in encoding temporal information and binding errors [43].

For each group comparison, we firstly performed a repeated-measurements analysis of variance (ANOVA), in which the dependent variable was either the T1 accuracy, P(T2|T1) for attention, AB index, or swap ratio as described above. The independent variables in the ANOVA were the genotype of APOE4 or MAPT, sex, and lag (lag is a within-subject factor while others are between-subject factors). The covariate was centered age (age – averaged age). Then, we have performed secondary group ANOVA tests for each sex separately. This time, the variables were unchanged, except that we removed sex in the ANOVA model. Greenhouse-Geisser corrections (GG corrections for short) were applied to those tests where non-sphericity issues were present.

Importantly, since our sample size is large, the data degrees of freedom are large. Such high data degrees of freedom can at least in part drive a significant finding [49]. Accordingly, we will report partial eta squared effect sizes throughout, which are not impacted by sample size in this way [49] and should be accurate when sample size is large.

Results

Genetic tests

Out of 392 participants, 385 participants were successfully genotyped for rs7412. Genotype CC N=344 (228 females), CT N=40 (27 females), and TT N=1 (1 females). Three tests of Hardy-Weinberg equilibrium were performed for all, male, and female participants respectively (x^2 = 0.02, 0.04, and 0.36 respectively, and all *P's* > 0.05). So, the genotype frequencies of rs7412 in our samples were consistent with Hardy-Weinberg equilibrium.

Out of 392 participants, 390 participants were successfully genotyped for rs429358. Genotype CC N=1 person (0 females), CT N=70 (48 females), and TT N=319 persons (213 females). Three tests of Hardy-Weinberg equilibrium were performed (x^2 = 1.97, 2.68, and 0.01 respectively, and all *P's* > 0.05). So, the genotype frequencies of rs429358 in our samples were consistent with Hardy-Weinberg equilibrium.

Out of 392 participants, 386 participants were successfully genotyped for rs242557, with genotype AA N=121 (77 females), AG N=193 (136 females), and GG N=72 (45 females). Three tests of Hardy-Weinberg equilibrium were performed for all three genetic groups according to MAPT (x^2 = 0.10, 1.29, and 1.12

respectively, and all *P's* > 0.05). So, the genotype frequencies of rs242557 in our samples were consistent with Hardy-Weinberg equilibrium.

Demographics

In the total of 392 participants, 261 are females. The mean and standard deviation of the participants' ages were 19.71 and 0.98 years respectively. The demographic data divided into each genetic group is shown in Table 1. We found no statistically significant difference in age, sex, and years of education between different risk groups defined by APOE and MAPT status.

Table 1. Demographics by Genotype

	APOE4		rs242557	
Category	Non-carrier	Carrier	G carrier	AA
Gender				
Male	108	20	84	44
Female	214	42	181	77
Education				
U1	174	33	143	66
U2	124	24	101	48
U3	14	3	11	5
U4	10	2	10	2
Age				
Mean	19.67	19.72	19.71	19.71
SD	0.97	0.99	0.99	0.97

Note. U1 to U4: 1st to 4th year undergraduates. Age was calculated as (participating date - birth date)/365.25.

APOE effects on T1

In the ANOVA test, the main effect of lag was significant: $F(8, 3023) = 306.844$, $P < .001$, $\eta^2 = .447$ [after GG correction, $F(7.101, 2691.461) = 306.844$, $P < .001$, $\eta^2 = .447$]. No other main effects or interactions were significant. The results remained the same after splitting the males and females into two separate groups in the secondary ANOVA tests. See Figure. 2 for more details. We noted that the T1 accuracy was generally low at lag-1 due to the short SOA of 50ms, but this finding is consistent with previous research [50]. Importantly, there was no statistically significant effect of APOE genotype on visual perception measured by the AB task.

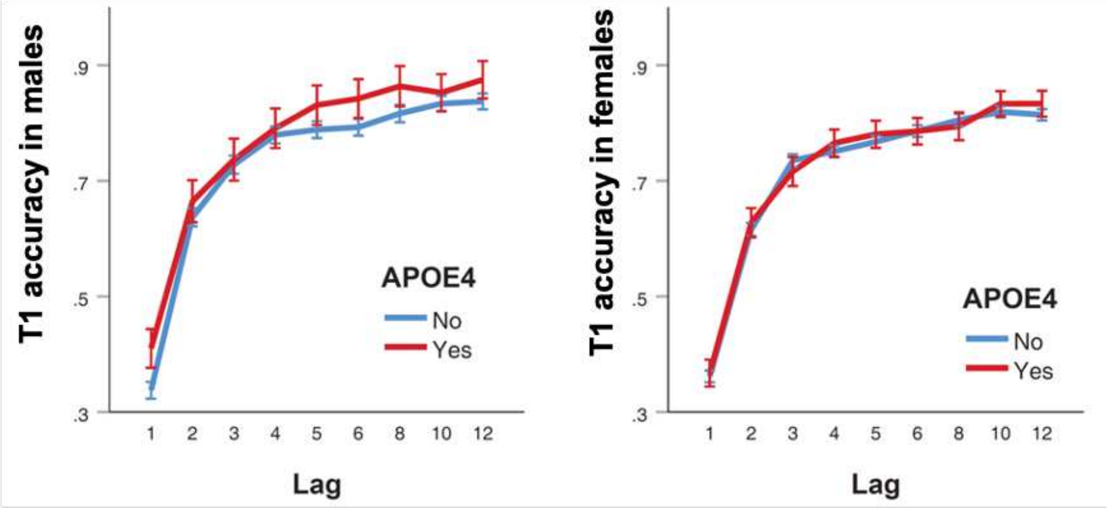

Figure. 2 The effects of APOE4 on T1 accuracy for males (left) and females (right) respectively. Error bars represent standard errors. X-axis represents lag and Y-axis represents probability of detecting T1. We found no group difference for APOE status suggesting that there was no significant effect of APOE on T1 accuracy.

MAPT effects on T1

In this ANOVA test, the main effect of lag was also significant: $F(8, 3048) = 534.303$, $P < .001$, $\eta^2 = .584$ [after GG correction, $F(7.112, 2709.828) = 534.303$, $P < .001$, $\eta^2 = .584$]. No other main effects nor interactions were significant. The results remained the same after splitting the males and females into two separate analyses. See Figure. 3 for more details. Like APOE, MAPT also did not change perception functioning in this task.

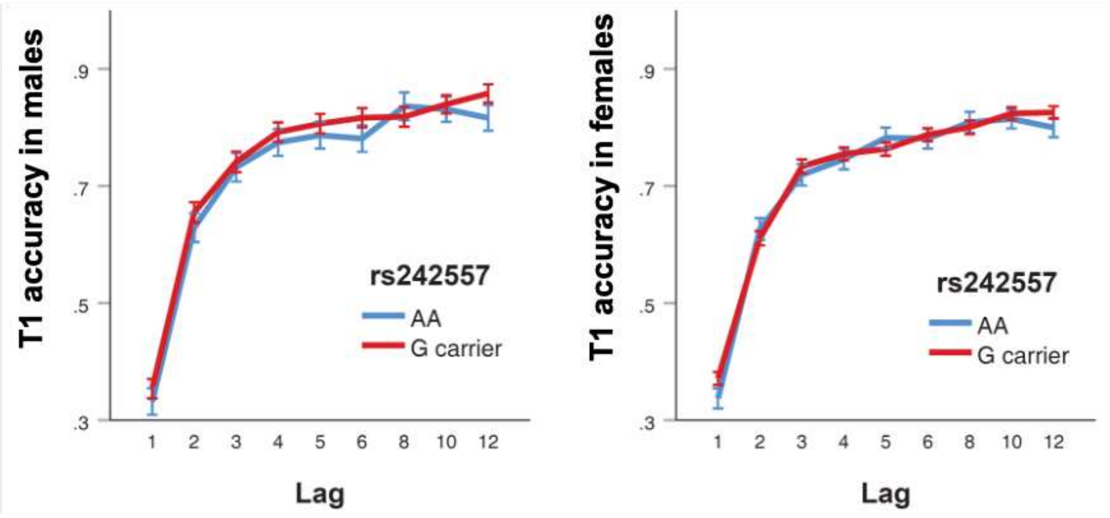

Figure. 3 The effects of MAPT (rs242557) on T1 accuracy for males (left) and females (right) respectively. Error bars represent standard errors. X-axis represents lag and Y-axis represents probability of detecting T1. Similar to the previous results in APOE, MAPT also did not change perception functioning in this task.

APOE effects on temporal attention

Unsurprisingly, in the ANOVA test, the main effect of lag was statistically significant: $F(8, 3016) = 47.543, P < .001, \eta^2 = .112$ [after GG correction, $F(6.313, 2380.005) = 47.543, P < .001, \eta^2 = .112$], suggesting that there was an AB effect as expected. We found that the main effect of APOE4 was statistically significant: $F(1, 377) = 10.545, P = .001, \eta^2 = .027$. The interaction of APOE4 and sex only showed an insignificant trend: $F(1, 377) = 3.415, P = .065, \eta^2 = .009$. The interaction of APOE4, sex and lag was significant: $F(8, 3016) = 2.454, P = .012, \eta^2 = .006$ [after GG correction, $F(6.313, 2380.005) = 2.454, P = .021, \eta^2 = .006$]. No other main effect or interaction was significant.

In the secondary ANOVA tests, for males, the main effect of APOE4 was significant: $F(1, 124) = 8.285, P = .005, \eta^2 = .063$. The interaction between APOE4 and lag was significant: $F(8, 992) = 2.907, P = .003, \eta^2 = .023$ [after GG correction, $F(6.267, 777.113) = 2.907, P = .007, \eta^2 = .023$]. The main effect of lag was also significant. For females, the main effect of lag was significant, but no other main effect or interaction was statistically significant. As shown in Figure. 4, the APOE4 effect on attention deployment was only significant in male participants.

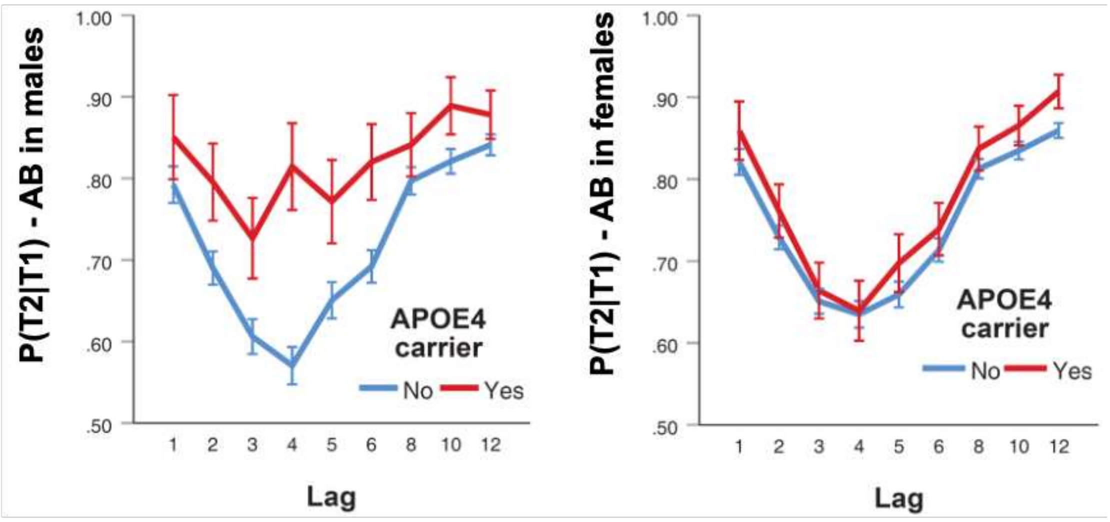

Figure. 4 The effects of APOE4 on T2 accuracy conditional on T1 for males (left) and females (right) respectively. Error bars represent standard errors. X-axis represents lag and Y-axis represents conditional probability of detecting T2 condition on T1. Male but not female APOE4 carriers had better AB performance, i.e., carriers were more likely to report T2 correctly after correctly reporting T1 than noncarriers.

MAPT effects on temporal attention

In this ANOVA test, the main effect of lag was significant: *F*(8, 3032) = 93.272, *P* < .001, η^2 = .197 [after GG correction, *F*(6.327, 2397.845) = 93.272, *P* < .001, η^2 = .197]. No other main effect or interaction was significant. In addition, in the secondary ANOVA tests, for males, the main effect of lag was significant, but no other main effect or interaction was significant. For females, the main effect of MAPT rs242557 was significant: *F*(1, 254) = 4.114, *P* = .044, η^2 = .016. The interaction between MAPT rs242557 and lag showed an insignificant trend: *F*(8, 2032) = 1.817, *P* = .069, η^2 = .007 [after GG correction, *F*(6.260, 1590.097) =

1.817, *P* = .089, η^2 = .007]. The main effect of lag was significant, but no other main effect or interaction was significant. As shown in Figure. 5, MAPT only significantly affected female participants in this task.

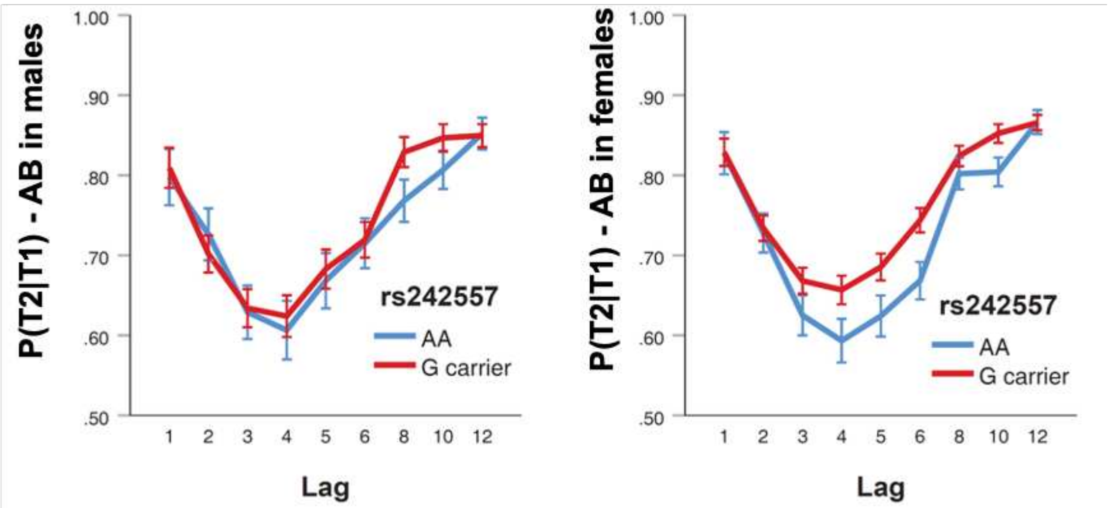

Figure. 5 The effects of MPAT (rs242557) on T2 accuracy for males (left) and females (right) respectively. Error bars represent standard errors. X-axis represents lag and Y-axis represents conditional probability of detecting T2 conditional on T1. Female but not male MAPT AA carriers had poorer AB performance than MAPT G carriers.

Interaction between APOE and MAPT on the AB index

We reanalysed the attention effect using the AB index. As previously discussed, it is more sensitive and powerful to test the interaction between two genetic risks. In this ANOVA test (lag is no longer an independent variable), the main effect of sex was significant: *F*(1, 370) = 5.902, *P* = .016, η^2 = .016. The main effect of APOE4 was significant: *F*(1, 370) = 4.370, *P* = .037, η^2 = .012. The main effect of MAPT rs242557 was significant: *F*(1, 370) = 4.201, *P* = .041, η^2 = .011. The interaction among APOE4 and sex was statistically significant: *F*(1, 370) = 14.813, *P* < .001, η^2 = .038.

In the secondary ANOVA tests, for males, the main effect of APOE4 was significant: *F*(1, 121) = 15.495,

$P < .001$, $\eta^2 = .114$. No other main effect or interaction was significant. For females, the main effect of MAPT rs242557 was significant: $F(1, 248) = 4.700$, $P = .031$, $\eta^2 = .019$. No other main effect or interaction was significant. As shown in Figure. 6, findings in this more sensitive analysis were consistent with those from the two previous analyses although no gene-gene interaction was found for the AB index.

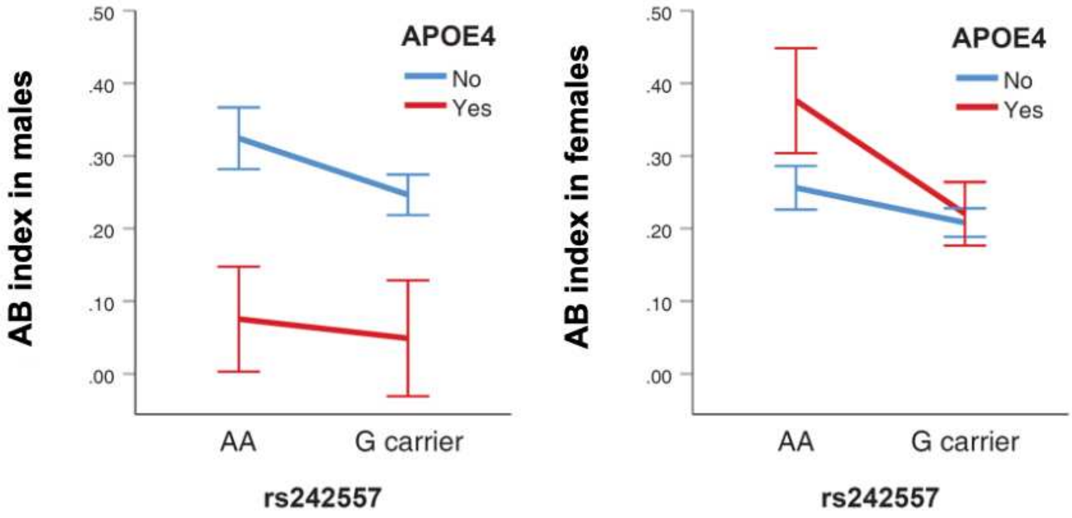

Figure. 6 The interaction effects of APOE4 and MPAT (rs242557) on attentional blink index for males (left) and females (right) respectively. Error bars represent standard errors. Y-axis represents the difference between conditional probabilities of detecting T2 conditional on T1 at lag 4 and lag 12. We found no APOE-MAPT interaction.

APOE effects on swaps

In the ANOVA test, the main effect of lag was significant: $F(8, 3032) = 250.988$, $P < .001$, $\eta^2 = .398$ [after GG correction, $F(3.437, 1302.522) = 250.988$, $P < .001$, $\eta^2 = .398$] but no other main effects nor interactions were significant. See Figure. 7 for more details.

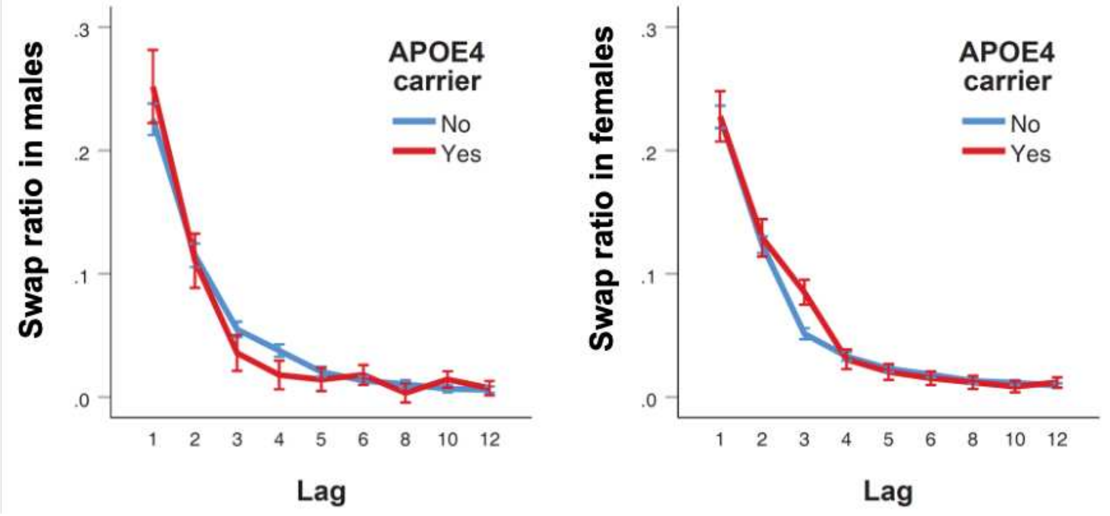

Figure. 7 The effects of APOE4 on swap ratio for males (left) and females (right) respectively. Error bars represent standard errors. X-axis represents lag and Y-axis represents probability of reporting T1 and T2 in the incorrect order.

MAPT effects on swaps

Like APOE, in this ANOVA test, the main effect of lag was also significant: *F*(8, 3048) = 399.328, *P* < .001, η^2 = .512 [after GG correction, *F*(3.420, 1302.915) = 399.328, *P* < .001, η^2 = .512], but no other main effects nor interactions were significant. See Figure. 8 for more details.

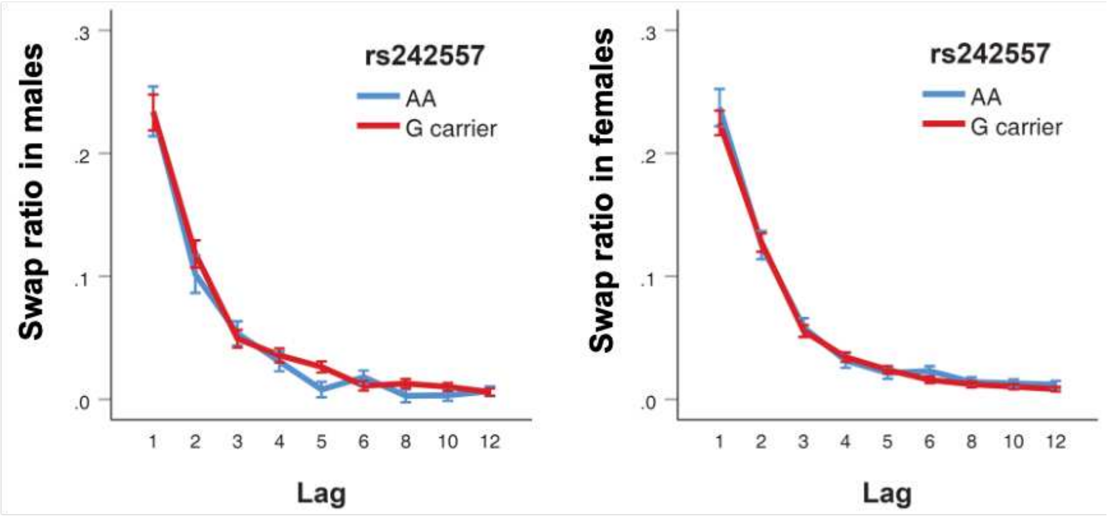

Figure. 8 The effects of MAPT (rs242557) on swap ratio for males (left) and females (right) respectively. Error bars represent standard errors. X-axis represents lag and Y-axis represents probability of reporting T1 and T2 in the incorrect order.

Discussion

In our study, we found a significant reduction in the AB effect or improved temporal attentional performance for APOE4 carriers, which is consistent with previous evidence of the antagonistic pleiotropy hypothesis supporting the improved attentional function in young adults [4]. However, we only found this beneficial effect in males but not in females. In most previous studies on older people, researchers found that APOE4 confers a greater risk of dementia and mild cognitive impairment in females than in males [51-53]. Opposite to our results, in a study on executive function and processing speed, the cognitively beneficial effect of APOE4 was found in young females rather than males [54]. However, a male-specific advantage of APOE4 on short-term memory was found in middle-aged individuals in another study [55]. In one of our own studies, sex differences in path integration and spatial navigation ability were found in middle-aged at-risk individuals without cognitive impairment [56]. We speculate that sex differences in neurotransmitter systems critical to attentional processing, such as acetylcholine (Ach) in the brain, where females have overall higher release than males , and different experimental methodologies discussed earlier may also play a role on these inconsistent sex differences [57].

For the other genetic risk factor of AD, MAPT rs242557 AA genotype, we found an increased AB effect or poorer attentional function in carriers but this time only in females. To the best of our knowledge, there is no known sex-specific cognitive bias associated with MAPT rs242557 genotype in the AB task, and as previously discussed, the effect of rs242557 genotype in general cognitive function, executive function, and attention in older adults is inconclusive in the literature too. In addition, although not statistically significant, there seems a nonsignificant trend suggesting an interaction between APOE and MAPT in AB especially in females (Figure. 6), i.e., carriers of both APOE4 and MAPT AA had the deepest blink in AB (larger AB index) suggesting a stronger interference between T1 and T2 or more limited attentional resources to correctly encode both targets. However, this finding should be interpreted with caution. Finally, we did not see any genetic effect on T1 accuracy or swaps (perceptual functioning and temporal memory encoding/binding), which was reported in older patients with dementia [45], suggesting that the early effects of these genetic risk factors are not merely due to limited cognitive resource but a variation in specific attentional control mechanisms.

We of course acknowledge that resource limitation is not the only possible explanation of the attentional blink phenomenon. The Simultaneous Type - Serial Token (STST) model [58] is a prominent theory of the AB, which has explained a large number of AB and related phenomena [59-61]. The theory also offers the possibility to provide a theoretical explanation of our findings. In the STST framework, a key driver of blink depth is the time to encode the T1. Specifically, the attentional blink is postulated to be caused by the process of encoding T1 “closing the gate” for working memory encoding on T2 (by withholding a transient attentional enhancement called the *Blaster*). This gate closing ensures that the encoding of T1 is not “contaminated” by the T2 entering that same encoding process, which would yield binding errors, such as features from T2 migrating to T1. Thus, the theory raises the possibility that a male APOE4 carrier encodes stimuli more rapidly into working memory than a male noncarrier, and similarly for a female G-carrier. Of course, such a hypothesis needs further investigation in other experimental paradigms, before it can be seen as more than speculative.

The current study was limited by its cross-sectional design. Thus, it is unable to reveal the dynamic changes of attentional function transitioning from early adulthood to midlife, during which distinctive cognitive impairments may start to occur. As age is one of the biggest risk factors of AD, and it is known that visual attention task performance is often age dependent [62, 63], future longitudinal studies will be able to address this limitation. The current study samples were heavily skewed towards participants with younger age because they present the majority in the university. Thus, future research should include older adults including those in middle age. Another limitation of the study was using a single test, the AB, although as previously discussed, it is a robust test for attention, nonetheless, sensitive and specific screening tests based on other visual tasks [64] and navigation tasks [56] have provided novel candidate tools for early detection of dementia and practical solutions for screening in multiple clinical and community settings. As evidence points towards AD pathology occurring before the symptom onset, this raises the question of whether these pathological changes can be detected in this pre-symptomatic stage. With the development of novel disease-modifying treatments for AD, such early detection would be highly advantageous by allowing for treatment to begin sooner before more irreversible neurodegeneration occurs thus improving outcomes. Additionally, detection of AD and its risk factors related changes earlier in life would allow individuals to make healthier lifestyle choices in order to reduce their risk of developing AD [65], so detection in early adulthood may also be beneficial. Accordingly, it is predicted that early detection and intervention could drastically reduce the worldwide AD burden, with models suggesting that delaying disease onset by as little as 1 year could reduce the global incidence of AD by up to 9.2 million in the year 2050 [66].

This study is also limited by the candidate gene approach with limited number of SNPs genotyped. This may miss other critical genetic factors influencing attention such as the tonic level of neurotransmitters including cholinergic systems. Moreover, only Chinese students were recruited into the study. Although this increased genetic similarity among participants, it also limited the generalizability of the our findings to other ethnic groups. In conclusion, we have found an ultra-early effect of AD related genetic risk factors (APOE and MAPT) that are linked to two cornerstones of AD pathology (amyloid-beta and tau) using a temporal attention task. The findings are generally consistent with previous research suggesting a 'beneficial' effect of APOE4 on attention and executive control, but only in males. The less studied gene MAPT however had an opposite effect than APOE in females. Finally, the study also highlighted sex differences in genetic risks as an important topic for future research.

Authors' contribution

JZ and LS designed the study and secured the funding. JZ did the programming. JZ, XH and HQ collected the data. JZ conducted the analyses. JZ, ZG and LS drafted the manuscript. CR, LS and JZ co-designed the PREVENT-Dementia study. XX, YL and DZ provided feedback on the data analysis and the manuscript. YH, HB, JOB provided feedback on the manuscript. LS provided oversight for the study.

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Conflict of Interest

The authors have no conflict of interest to report.

Data Availability

The data supporting the findings of this study are available on request from the corresponding authors. The data are not publicly available due to privacy or ethical restrictions.

Ethics approval

This study was approved by the Ethic Committee of Psychological Research at Southwest University.

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