**Supplementary Material**

**SM methods**

**Subjects**

The subjects, to be considered for inclusion, had to finish neuropsychological assessment, event-related potential (ERP) measurement, and structural magnetic resonance imaging (MRI) scan in Henan Mental Hospital, the Second Affiliated Hospital of Xinxiang Medical University.

This study initially recruited 291 elderly individuals, through normal community health screening in Xinxiang, Henan. After the clinical screening, a total of 92 subjects signed written informed consents and further finished neuropsychological assessment, including 44 amnestic mild cognitive impairment (aMCI) and age, gender well-matched 48 normal controls (NC). The inclusion criteria of clinical screening included: (1) aged between 50 and 80 years, (2) biological right-handed, (3) ≥ 8 years of education, (4) absence of dementia, symptoms that were not sufficient to meet the criteria of the National Institute of Neurological and Communicative Disorders and Stroke or the Alzheimer’s disease (AD) and Related Disorders Association criteria for AD, (5) no history of known stroke (modified Hachinski score of > 4), alcoholism, head injury, Parkinson’s disease, epilepsy, major depression (excluded by Hamilton depression rating scale), or other neurological or psychiatric illness, (6) no severe visual or hearing loss, (7) no MRI scan contraindications. Finally, 76 subjects (38 aMCI, 38 NC) finished the ERP measurement and structural MRI scan. Of these subjects, 4 aMCI and 4 NC subjects were excluded due to excessive signal artifacts of electroencephalogram (EEG). The remaining 34 aMCI and 34 NC subjects were included in final statistical analyses.

**Neuropsychological assessment**

Each subject underwent a standardized clinical interview and a comprehensive neuropsychological assessment that were performed by neurologists (Drs. Gu, and Gao), including Mini-Mental State Examination (MMSE), Mattis Dementia Rating Scale (MDRS), Auditory Verbal Learning Test-immediate recall (AVLT-IR), Auditory Verbal Learning Test-5-min delayed recall (AVLT-5-min-DR), Auditory Verbal Learning Test-20-min delayed recall (AVLT-20-min-DR), Logical Memory Test-immediate recall (LMT-IR), Logical Memory Test-20-min delayed recall (LMT-20-min-DR), Rey-Osterrieth Complex Figure Test (ROCFT), Rey-Osterrieth Complex Figure Test-20-min delayed recall (ROCFT-20min-DR), Trail-Making Tests A and B (TMT-A and B), Digital Symbol Substitution Test (DSST), Digit Span Test (DST), Stroop Color and Word Test A, B, and C, Verbal Fluency Test (VFT), Semantic Similarity (Similarity) test, and Clock Drawing Test (CDT). These tests were used to evaluate general cognitive function, episodic memory, information processing speed, executive function, and visuospatial function, respectively.

**Process for Determining the APOE Genotype**

A polymerase chain reaction-based restriction fragment length polymorphism (PCR-RFLP) assay was applied to detect the alleles of rs7412 and rs429358, respectively. The amplification reaction system contained 1 × GC buffer I (TAKARA), 2.0-mM Mg2+, 0.2-mM dNTP, 1-unit HotStarTaq polymerase (Qiagen Inc.), 1-µl genomic DNA and 1-µl (2-µM) primer for each allele (for rs429358, forward primer: AGGGCGCTGATGGACGAGAC, reverse primer: GCCCCGGCCTGGTACACT; for rs7412, forward primer: GGCGCGGACATGGAGGAC, reversed primer: GCCCCGGCCTGGTACACT). PCR cycling conditions were set as follows: 1) 95ºC lasted for 15 min; 2) Eleven cycles were performed, and each of which included a) 94ºC for 20s, b) keeping the temperature at 0.5 ºC below the melting temperature for 40s, c) 72ºC for 1min 40s; 3) Another 24 cycles were performed, and each of which included a) 94ºC for 20s, b) keeping the temperature at 6ºC below the melting temperature for 40s, c) 72ºC for 1.5min; 4) 72ºC for 2 min. Amplification was carried out on 2720 Thermal Cycler (ABI). Then, 10-µl amplified product was digested with 1-unit restriction endonuclease (AflⅢ for rs429358 and HaeⅡ for rs7412) at 37ºC overnight. Finally, the digested product was diluted tenfold and analyzed by capillary electrophoresis to detect the alleles of rs429358 and rs7412. As a result, the APOE genotype was determined by the haplotype of rs429358 and rs7412. APOE ε2 allele was recognized by rs429358-T and rs7412-T, APOE ε3 allele was identified by rs429358-T and rs7412-C, and APOE ε4 allele was defined by rs429358-C and rs7412-C.

**Statistical analysis**

**Demographic and neuropsychological data**

To increase statistical power by reducing random variability, this study composited the neuropsychological tests into 4 cognitive domains and transformed the raw scores into 4 composite Z scores, as previously described ([Xie et al., 2012](#_ENREF_1)). First, for each neuropsychological test, the individual raw scores were transformed to Z scores, according to the mean and standard deviation of the scores for all subjects. Notably, for tests measured in time, including TMT-A, TMT-B, Stroop A, Stroop B, and Stroop C, the raw scores were defined as the reciprocal of the time required for the test. Then, each cognitive domain’s composite Z score was determined by averaging the Z scores related to the tests. We divided these tests into 4 cognitive domains: episodic memory (3 tests, including AVLT-20-min-DR, LMT-20-min-DR, and ROCFT-20-min-DR), information processing speed (4 tests, including DSST, TMT-A, Stroop A, and Stroop B), visuospatial function (2 tests, including CFT and CDT), and executive function (5 tests, including VFT, DST, TMT-B, Stroop C, and Similarity).

**Group effects on the correlation of P300 latency with cognitive performance or grey matter volume.**

We investigated if the group factor showed any effect on the correlation of P300 latency with cognitive performance or the grey matter (GM) volume. Detailed method is provided below.

First, we employed a linear regression model to examine the effects of group, P300 latency, and their interaction on information processing speed (Z score), as shown below:

where is the information processing speed (Z score) for each subject across the two groups; β0 is the intercept of the fitting line; β1, β2, β4, β5, β6 and β7 are the effects of P300 latency, group, age, gender, education years, and APOE genotype, respectively; β3 represents the interaction between group and P300 latency; ε denotes the random errors.

Second, we employed a linear regression model to examine the effects of group, P300 latency, and their interaction on the Stroop A score (Z score), as shown below:

where is the Stroop A score (Z score) for each subject across the two groups; β0 is the intercept of the fitting line; β1, β2, β4, β5, β6 and β7 are the effects of P300 latency, group, age, gender, education years, and APOE genotype, respectively; β3 represents the interaction between group and P300 latency; ε denotes the random errors.

Third, we employed a voxel-based multiple linear regression model to examine the effects of group, P300 latency, and their interaction on the GM volume within brain regions showing significant group difference, as shown below:

where *GMV* is GM volume map for each subject across the two groups; β0 is the intercept of the fitting line; β1, β2, β4, β5, β6, β7 and β8 are the effects of P300 latency, group, age, gender, education years, APOE genotype and total intracranial volume, respectively; β3 represents the interaction between group and P300 latency; ε denotes the random errors.

**Results**

**Group effects on the correlation of P300 latency with cognitive performance or GM volume.**

We found no interaction between group and P300 latency on information processing speed (Z score) or Stroop A score (Z score) (see Table S2 and S3). In addition, we found no interaction between group and P300 latency on the GM volume within brain regions showing significant group difference.

**Table S1**

**Comparison of clinical features and neuropsychological data between aMCI and NC groups**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Items | aMCI  (N=34) | NC  (N=34) | t values | *p* values |
| Age (years) | 61.09 (5.52) | 60.15 (5.65) | 0.70 | 0.49 |
| Gender (males/females) | 12/22 | 17/17 | -1.50 | 0.22 |
| Education (years) | 9.60 (1.49) | 11.13 (1.93) | -3.67 | 0.000\* |
| APOE (ε4+/ε4-) | 6/28 | 4/30 | -0.47 | 0.49 |
| **MDRS-2 raw scores** | | | | |
| Attention | 36.32 (0.73) | 36.65 (0.54) | -2.08 | 0.04 |
| Initiation/Preservation | 36.06 (1.86) | 36.18 (1.60) | -0.28 | 0.78 |
| Construct | 5.91 (0.29) | 6.00 (0.00) | -0.18 | 0.08 |
| Conceptual | 37.53 (1.64) | 38.00 (1.13) | -1.38 | 0.17 |
| Memory | 21.35 (1.67) | 22.68 (1.17) | -3.79 | 0.000\* |
| Total | 137.21 (3.35) | 139.50 (2.31) | -3.29 | 0.002\* |
| **Episodic memory** | | | | |
| AVLT-20min DR (raw score) | 2.65 (1.10) | 6.62 (1.71) | -11.41 | 0.000\* |
| AVLT-20min DR (*Z* score) | -0.83 (0.45) | 0.80 (0.70) | -11.41 | 0.000\* |
| LMT-20min DR (raw score) | 2.96 (2.04) | 5.97 (2.06) | -6.06 | 0.000\* |
| LMT-20min DR (*Z* score) | -0.59 (0.80) | 0.58 (0.80) | -6.06 | 0.000\* |
| CFT-20min DR (raw score) | 12.52 (6.35) | 19.16 (5.98) | -4.44 | 0.000\* |
| CFT-20min DR (*Z* score) | -0.50 (0.91) | 0.45 (0.85) | -4.44 | 0.000\* |
| **Visuospatial function** | | | | |
| CDT (raw score) | 8.38 (0.74) | 9.09 (0.75) | -3.90 | 0.000\* |
| CDT (*Z* score) | -0.42 (0.91) | 0.44 (0.92) | -3.90 | 0.000\* |
| CFT (raw score) | 34.43 (3.50) | 35.74 (0.67) | -2.14 | 0.04 |
| CFT (*Z* score) | -0.27 (1.37) | 0.25 (0.26) | -2.14 | 0.04 |
| **Information processing speed** | | | | |
| DSST (raw score) | 33.12 (8.04) | 40.50 (8.32) | -3.72 | 0.000\* |
| DSST (*Z* score) | -0.41 (0.91) | 0.43 (0.94) | -3.72 | 0.000\* |
| TMT-A (second) | 78.71 (27.73) | 58.62 (16.08) | 3.65 | 0.001\* |
| TMT-A (*Z* score) | -0.40 (0.88) | 0.41 (0.98) | -3.56 | 0.001\* |
| Stroop A (second) | 29.09 (8.06) | 25.62 (3.89) | 2.26 | 0.028 |
| Stroop A (*Z* score) | -0.21 (1.02) | 0.31 (0.85) | -2.24 | 0.028 |
| Stroop B (second) | 42.65 (10.59) | 39.88 (7.10) | 1.26 | 0.21 |
| Stroop B (*Z* score) | -0.09 (1.10) | 0.13 (0.90) | -0.89 | 0.38 |
| **Executive function** |  |  |  |  |
| VFT (raw score) | 22.74 (5.50) | 23.50 (5.34) | -0.58 | 0.56 |
| VFT (*Z* score) | -0.04 (1.01) | 0.10 (0.98) | -0.58 | 0.56 |
| DST-backward (raw score) | 3.85 (0.93) | 4.44 (1.21) | -2.25 | 0.028 |
| DST-backward (*Z* score) | -0.27 (0.85) | 0.27 (1.11) | -2.25 | 0.028 |
| TMT-B (second) | 193.38 (66.91) | 146.50 (44.41) | 3.40 | 0.001\* |
| TMT-B (*Z* score) | -0.35 (0.77) | 0.38 (1.10) | -3.19 | 0.002\* |
| Stroop C (second) | 83.12 (27.17) | 74.41 (16.45) | 1.60 | 0.12 |
| Stroop C (*Z* score) | -0.16 (0.98) | 0.21 (1.00) | -1.55 | 0.13 |
| Similarity (raw score) | 15.44 (3.64) | 18.68 (2.99) | -4.01 | 0.000\* |
| Similarity (*Z* score) | -0.45 (1.00) | 0.44 (0.82) | -4.01 | 0.000\* |

Data are presented as mean ± stand deviation (SD). Abbreviations: aMCI, amnestic mild cognitive impairment; NC, normal controls; MDRS-2, Mattis Dementia Rating Scale-2; AVLT-20min DR, Auditory Verbal Learning Test-20-minute delayed recall; LMT-20min DR, Logical Memory Test-20-minute delayed recall; CFT-20min DR, Rey-Osterrieth Complex Figure Test-20-minute delayed recall; CDT, Clock Drawing Test; CFT, Rey-Osterrieth Complex Figure Test; DSST, Digital Symbol Substitution Test; TMT-A, Trail Making Test-A; Stroop, Stroop Color and Word Test; VFT, Verbal Fluency Test; DST, Digit Span Test; TMT-B, Trail Making Test-B; Similarity, Semantic Similarity Test.

\*Significant differences were found among aMCI patients and NC subjects. *p* values were obtained by student t-test. Bonferroni correction for multiple comparisons was used for cognitive scores with the significance level considered at *p* < 0.0025 (*p* = 0.05/20 cognitive scores). For age, gender, education, APOE, a statistical threshold was p < 0.05.

**Table S2 Effects of group, P300 latency, and their interaction on information processing speed (Z score)**

|  |  |  |
| --- | --- | --- |
| Predictors | Regression coefficients (95% CI) | *p* values |
| P300 latency | -0.002 (-0.006 to 0.002) | 0.320 |
| group | 0.305 (-1.680 to 2.291) | 0.759 |
| group×P300 latency | -0.002 (-0.007 to 0.003) | 0.473 |
| age | -0.023 (-0.055 to 0.010) | 0.172 |
| gender | -0.125 (-0.486 to 0.235) | 0.489 |
| education | 0.054 (-0.052 to 0.161) | 0.311 |
| APOE | 0.107 (-0.399 to 0.613) | 0.675 |

**Table S3 Effects of group, P300 latency, and their interaction on Stroop A (Z score)**

|  |  |  |
| --- | --- | --- |
| Predictors | Regression coefficients (95% CI) | *p* values |
| P300 latency | -0.002 (-0.007 to 0.002) | 0.303 |
| group | 1.549 (-0.984 to 4.083) | 0.226 |
| group×P300 latency | -0.005 (-0.012 to 0.002) | 0.132 |
| age | 0.000 (-0.041 to 0.042) | 0.989 |
| gender | 0.025 (-0.436 to 0.485) | 0.915 |
| education | -0.019 (-0.155 to 0.117) | 0.779 |
| APOE | 0.308 (-0.338 to 0.953) | 0.345 |



Fig S1. Schematic diagram of data collection and analysis

Abbreviations: aMCI, amnestic mild cognitive impairment; NC, normal controls; MRI, magnetic resonance imaging; EEG, electroencephalogram; ERP, event-related potential; GM, grey matter.



Fig S2. Correlation of P300 latencies with information processing speed (Z scores) (A) and Stroop A scores (Z scores) (B) in the aMCI and NC groups, respectively. Abbreviations: aMCI, amnestic mild cognitive impairment; NC, normal controls; Stroop, Stroop Color and Word Test.

Xie, C., Bai, F., Yu, H., Shi, Y., Yuan, Y., Chen, G., . . . Li, S. J. (2012). Abnormal insula functional network is associated with episodic memory decline in amnestic mild cognitive impairment. *Neuroimage, 63*(1), 320-327. doi: 10.1016/j.neuroimage.2012.06.062