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SORL1 rs1699102 polymorphism modulates age-related cognitive decline and gray matter volume reduction in non-demented individuals

He Li, PhD[#1,4], **Chenlong Lv, PhD**[#3], **Caishui Yang, BD**[#2,4], **Dongfeng Wei, MD**[1,4], **Kewei Chen, PhD**[5], **Shaowu Li, MD**[6], and **Zhanjun Zhang, MD**[2,4]

[1] Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences, Beijing, P.R. China

[2] State Key Laboratory of Cognitive Neuroscience and Learning and IDG/McGovern Institute for Brain Research, Beijing Normal University, Beijing, P. R. China

[3] Consulting Center of Biomedical Statistics, Academy of Military Medical Sciences, Beijing, P. R. China

[4] BABRI Centre, Beijing Normal University, Beijing, P. R. China

[5] Computational Image Analysis Banner Alzheimer's Institute, Phoenix, AZ, USA

[6] Dept of Functional Neuroimaging, Beijing Neurosurgical Institute, Beijing, P. R. China

[#] These authors contributed equally to this work.

Abstract

Background—*SORL1* rs1699102 is associated with the risk of late-onset Alzheimer's disease (AD). However, the effects of this SNP on cognition and brain structure during normal aging are unclear. This study aims to examine the effects of the rs1699102 polymorphism on age-related cognitive decline and cortical gray matter reduction in Chinese Han population.

Methods—780 non-demented adults completed a battery of neuropsychological tests. High-resolution T1-weighted structural magnetic resonance imaging (MRI) data from 89 of these subjects were also collected using a Siemens Trio 3.0 Tesla scanner.

Results—The T allele carriers displayed an accelerated age-related change in episodic memory and processing speed tests relative to the CC genotype. A similar pattern was observed in the age-

Correspondence to: Zhanjun Zhang, MD, BABRI Centre, State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing 100875, China, Tel/Fax: +86 1058802005, zhang_rzs@bnu.edu.cn and Shaowu Li, MD, Dept of Functional Neuroimaging, Beijing Neurosurgical Institute, Beijing 100050, China, Tel/Fax: +86 1067096784, lys5@sina.com.

Author's contributions

He Li, Chenlong Lv and Caishui Yang analyzed the data and drafted the manuscript. Dongfeng Wei assisted with the data collection and analysis. Kewei Chen advised on biostatistical methodology and critically reviewed the manuscript. Zhanjun Zhang conceived the original idea for the study. Zhanjun Zhang and Shaowu Li supervised in the conception, and revised the manuscript. All authors read and approved the final manuscript.

Disclosure statement

The authors of this manuscript have no conflicts of interest to declare.

related gray matter volume (GMV) reduction of the right middle temporal pole. The GMV in this region was significantly positively correlated with the episodic memory scores.

Conclusions—The *SORL1* gene rs1699102 polymorphism has been found to be associated with age-related cognitive decline and GMV reduction of the right middle temporal pole in older adults. These findings elucidate how the *SORL1* variants shape the neural system to modulate age-related cognitive decline and support the hypothesis that *SORL1* may represent a candidate gene for late-onset AD.

Keywords

SORL1; cognitive decline; gray matter volume; non-demented elderly; Chinese

1. Introduction

Genetic factors play important roles in the development of late-onset Alzheimer's disease (AD). The apolipoprotein E (*ApoE*) ε4 allele is the most prominent susceptibility gene for AD [1]. In recent years, many more genes have been implicated to increase the risk of AD and shown to negatively impact cognition to varying degrees at very early stage of AD and even in cognitively intact elders [2, 3].

Sorting protein-related receptor with A-type repeats (SorLA, also known as LR11), a member of the low-density lipoprotein receptor family of *ApoE* receptors, has been identified to modulate amyloid precursor protein (APP) processing and amyloid-β (Aβ) production [4, 5]. Polymorphisms in the neuronal sortilin-related receptor (*SORL1*) gene that encodes SorLA have been implicated in late-onset AD [4, 6]. Evidence from an autopsy study showed that a *SORL1* haplotype in the 3' gene region that consists of a single nucleotide polymorphism (SNP) rs1699102 is associated with poor receptor expression in the brain of AD patients [7]. Although the risk allele might not be consistent across the different ethnic groups [4], the SNP rs1699102 and haplotypes that encompass this SNP have been found to be associated with a risk for AD [4, 8, 9].

In addition to the reported AD risk, the *SORL1* gene has been implicated in the relationship between its variants and cognitive abilities in non-demented subjects [10, 11]. Reynolds and colleagues found that several *SORL1* SNPs were associated with cognitive change trajectories in older adults [12]. Conversely, Liu and colleagues failed to find any significant association between the rs1699102 polymorphism and cognitive function [13]. To our knowledge, the relationship of this SNP with age-related cognitive changes in older adults remains inconclusive.

Recent brain magnetic resonance imaging (MRI) studies have revealed that several *SORL1* variants are associated with hippocampal atrophy, the microstructural integrity of the fronto-temporal white matter tracts and other AD-related neurodegenerative changes [14-16]. To date, only one study has reported a significant association between the haplotypes in the region of SNP rs1699102 and hippocampal atrophy, as well as general cerebral atrophy in AD patients and unaffected siblings [16]. The rs1699102 effects on the whole-brain and additional brain regions have yet to be reported in the literature. Such data on normal aging

will elucidate the neural substrates underlying the rs1699102-related risk of developing late-onset AD.

In the present study, 780 cognitively normal subjects completed a battery of neuropsychological tests, and high-resolution structural MRI on 89 of these subjects were collected to examine the effects of the *SORL1* gene rs1699102 polymorphism on age-related cognitive decline and cortical gray matter volume (GMV) reduction in a large cohort of non-demented elderly Han Chinese. A voxel-based morphometry (VBM) analysis was used to assess regional GMV. We hypothesized that the SNP rs1699102 might modulate an age-related reduction in the GMV.

2. Methods

2.1 Participants and neuropsychological measures

This study included 780 native Chinese subjects from the BABRI (Beijing Aging Brain Rejuvenation Initiative) database. Details of participant selection have been previously described in our previous paper [17]. Participants were included in this study if they met the following criteria: (1) aged older than 50 years; (2) had received 6 years or more of education; (3) a score of no less than 24 on the Mini-Mental-Status Examination-Chinese version (MMSE) [18]; (4) no history of taking psychoactive medications; (5) no large vessel disease, such as cortical or subcortical infarcts and watershed infarcts; (6) no history of addictions, neurologic or psychiatric diseases, or treatment that would impair cognitive function. Participants meeting the following criteria were excluded from the MRI study: (1) unable to fulfill the physical demands of the MR scanning; (2) history of neurologic, psychiatric, or systemic illnesses effecting cerebral function, including serious vascular diseases, head trauma, tumor, current depression, alcoholism, and epilepsy. Written informed consent was obtained from each participant. The study was approved by the Institutional Review Board of Beijing Normal University.

To evaluate the general mental status and other cognitive function, participants underwent a series of neuropsychological tests involving 5 cognitive domains. The general mental status was assessed with the MMSE. The episodic memory tests consisted of the Auditory Verbal Learning Test (AVLT) [19] and Recall component of Rey-Osterrieth Complex Figure Test (ROCF) [20]. The attention and processing speed tests consisted of the Symbol Digit Modalities Test (SDMT) [21] and Trail Making Test A (TMT-A) [22]. The visual-spatial tests consisted of the Copy component of ROCF and Clock-Drawing Test (CDT) [23]. The language ability tests consisted of the Boston Naming Test (BNT) [24] and Category Verbal Fluency Test (CVFT) [25]. The executive function was tested using the Trail Making Test B (TMT-B) [22] and Stroop Color-word Test (Stroop) [26]. The demographic information and neuropsychological characteristics based on the SORL1 genotypes are shown in Table 1.

2.2 SORL1 genotyping

Custom Taqman SNP Genotyping Assays (Applied Biosystems, Foster City, USA) were used to prescreen for the rs1699102 genotype in the participants. An additional two SNPs, rs429358 and rs7412, which jointly define the APOE ε2 (with haplotype of rs429358-

rs7414: T-T), ε3 (T-C), and ε4 alleles (C-C), were also genotyped [27]. The sample success rate for all of SNPs was 100%, and the reproducibility of all genotyping was 100% according to a duplication analysis of at least 10% of the genotypes. The rs1699102 genotyping indicated 163 T allele carriers (including 11 TT carriers and 152 CT carriers) and 617 CC homozygotes.

2.3 MRI data acquisition

The MRI data were collected from 37 subjects with the CT/TT genotypes and 52 subjects with the CC genotype using a Siemens Trio 3.0 Tesla scanner at the Imaging Center for Brain Research, Beijing Normal University and included 3D T1-weighted MRI scans. The high-resolution T1-weighted structural images were obtained using magnetization-prepared rapid gradient-echo sequences with the following parameters: 176 sagittal slices, slice thickness = 1 mm, repetition time (TR) = 1900 ms, echo time (TE) = 3.44 ms, field of view (FOV) = 256 × 256 mm^2, acquisition matrix = 256 × 256.

2.4 Structural image preprocessing

The individual structural images (3D T1-weighted anatomical images) of all subjects were obtained using the VBM8 toolbox of Statistic Parametric Mapping (SPM) (http://dbm.neuro.uni-jena.de/vbm/). The images were bias-corrected, tissue classified, and normalized to the MNI-space using nonlinear only transformations to compare the relative differences in the regional GMV [28].

The homogeneity of gray matter (GM) images was examined using the covariance structure of each image with all other images, which helped to identify outliers. As a result, seven extreme outliers that showed anatomical abnormalities or artifacts were identified and excluded. The remaining 82 images were employed in the subsequent analyses. The modulated GM images were smoothed with a Gaussian kernel of 8 mm FWHW. A general linear model (GLM) using the individual GM images with gender, education and APOE genotype as covariates was constructed to test the interaction between genotypes and age with SPM ($P < 0.001$, uncorrected). To correct for multiple comparisons, GM clusters with a false discovery rate (FDR) corrected $P < 0.05$ were considered significant. The GMV were extracted from the voxels in the whole cluster for the subsequent correlation analyses.

2.5 Statistical Analysis

The data were subjected to a Hardy-Weinberg equilibrium test using the Plink program [29]. The differences between the SNP rs1699102 T allele carriers and non-carriers were assessed with the Pearson χ^2 test for gender and *APOE* ε4 status, and a two-sample t-test was used for age and education. The GLM was applied to determine the effect of the interaction between genotypes and age on neuropsychological tests with gender, education and *APOE* ε4 status as covariates. Sensitivity analyses were applied to confirm the stability of effect. Spearman partial correlation analyses were used to investigate the relationship between the significantly interactional GM regions and the neuropsychological scores after adjusting for the covariates, such as rs1699102 genotypes (only for the global partial correlation analysis), age, gender, education and *APOE* ε4 status. All statistical analyses were performed using the SAS 9.3 software (SAS Institute, Cary, NC). A P value <0.05 was considered significant.

3. Results

3.1 Demographics and neuropsychological test results

The SNP rs1699102 did not deviate from the Hardy-Weinberg equilibrium in the total sample ($P > 0.05$). Table 1 lists the demographics and neuropsychological test scores of subjects stratified by the *SORL1* genotypes. The age, gender, education, or *APOE* ε4 status did not significantly differ between the two groups. Notably, AVLT-delay recall, AVLT-total, ROCF Recall and the TMT-A time showed a significant age × group interaction, and sensitivity analyses in which the 11 TT participants were excluded from the GLMs did not change the results. Specifically, the T allele carriers displayed a faster age-related change (decrease in AVLT-delay recall, AVLT-total and ROCF Recall, increase in TMT-A time) in the scores relative to the CC genotype. The analysis of the main group effect failed to produce remarkable results.

3.2 The interactive effects between rs1699102 variants and age on the GMV

We examined the interaction of the GMV between age and groups in a sub-sample that included 33 subjects carrying CT/TT alleles and 49 subjects carrying CC allele. The gender, education, and *APOE* ε4 status were matched between genotypes. According to the threshold of expected cluster size (90) obtained from the SPM results, we found that several regions exhibited a notably different rate of change of the GMV with aging between the two groups (Table 2, Figure 1). After FDR correction for multiple comparisons, only the right middle temporal pole (MTP) (Figure 2A) retained a significant group × age interaction effect on the GMV (Cluster Size = 63, FDR-corrected, $P < 0.05$), which demonstrated a difference in the regression slope between volume and age (Figure 2B). The GMV of this cluster within the CT/TT group decreased with age, while the CC group did not show similar effect. No regions could survive the multiple comparison correction during the analysis of the main group effect.

3.3 The relationships between the GMV and cognitive tests

The GMV extracted from significant interaction areas were employed in the following partial correlation analyses. The results showed that the GMV in the right MTP significantly positively related to the AVLT-delay recall ($r = 0.25$, $P = 0.028$) and the AVLT-total ($r = 0.30$, $P = 0.008$) scores. Furthermore, significant correlations with AVLT-delay recall ($r = 0.56$, P = 0.002) and AVLT-total ($r = 0.42$, P = 0.023) were also observed in the CT/TT group. Nevertheless, the two memory indicators of the CC group did not significantly correlate with GMV in the right MTP (AVLT-delay recall: $r = 0.04$, $P = 0.771$, AVLT-total: $r = 0.14$, $P = 0.346$). To adjust for the covariates, the residual was calculated to display the correlation between the neuropsychological tests and the GMV (Figure 3) [30]. Spearman partial correlation analyses were applied because of the non-normal distribution of AVLT-delay recall ($P = 0.0077$) and AVLT-total ($P = 0.0459$) scores.

4. Discussion

In this study, we first examined the effects of the *SORL1* gene rs1699102 polymorphism on age-related cognitive decline and cortical GMV reduction in a non-demented elderly

Chinese Han population. Some studies have investigated the relationship between the variants in the *SORL1* gene and cognitive function. However, the findings were somewhat mixed [10, 11, 13, 31]. Several demographic factors may modulate the effects of *SORL1* on cognitive abilities, which could cause these discrepant findings. Aging is a well-known risk factor for developing AD and cognitive impairment. Previous studies have suggested that age may interact with other genetic factors to affect cognition during aging [32]. Reynolds and colleagues first found that several *SORL1* SNPs are associated with cognitive change trajectories in older adults across multiple domains, including the spatial domain, episodic memory and verbal abilities [12]. Unfortunately, the SNP rs1699102 was excluded from the analysis in their study because of genotyping failure. In the current study, the polymorphism was found to be associated with age-related cognitive decline, primarily in episodic memory and processing speed. The performance of the AVLT, ROCF Recall and TMT-A tests in the T allele carriers declined at a faster rate compared with the CC group. An impairment in episodic memory is the primary symptom of AD and amnestic mild cognitive impairment and can be used to predict the likelihood of progression to dementia [33]. The speed of cognitive processing is considered a fundamental part of the cognitive system. A decrease in the processing speed impairs the fluid cognitive abilities [34]. Our findings suggest that the T allele of the rs1699102 polymorphism may be associated with a steeper age-related decline in cognitive function and a higher risk of AD. This hypothesis is consistent with a study in Chinese subjects, which reported that the T allele is more abundant in AD than in controls, although this difference is not significant [9]. The relationship of rs1699102 polymorphism with cognitive aging and AD requires further confirmation in other ethnic groups as well as a larger sample of the Chinese Han population.

Global or regional GM atrophy is a common change during aging that seems to be related to the impairment of multiple cognitive domains. In the current study, the rs1699102 polymorphism was found to be associated with the age-related reduction of the right MTP. A faster volume reduction of this region was observed in carriers of the T allele than in CC genotype carriers, with similar trends in several frontal, temporal and limbic regions (but not significant after correction for multiple comparisons). The temporal pole was atrophied in patients with AD [35]. The right temporal pole is believed to store personal memory, and showed activated during the discrimination of familiar faces and scenes from unfamiliar ones, and this region is likely involved in the recognition of familiar objects [36]. Moreover, the right anterior temporal pole activation was observed to reflect the psychological set associated with emotional memory retrieval [37]. In our study, the GMV in the right MTP and the episodic memory scores were found to significantly associate in all the subjects, and this relationship was still significant in the CT/TT carriers. Our findings suggest that non-demented elderly Han Chinese carriers of the rs1699102 T allele are at a higher risk of GM atrophy in the right MTP than individuals homozygous for the C allele, and this risk may be associated with the poorer performance of episodic memory tests. This association may explain the impairment of episodic memory in the T-allele carriers.

To our knowledge, only one study has investigated the effect of the *SORL1* gene rs1699102 polymorphism on brain volume and did not find a significant relationship between this SNP and any of the MRI measures, including general cerebral atrophy, hippocampal atrophy, white matter hyperintensities and overall cerebrovascular disease [16]. However, the

haplotypes that encompass the SNP rs1699102 were associated with hippocampal atrophy and general cerebral atrophy. Similar to their findings, the regional volume did not differ between genotype groups in our study, which may suggest that this SNP only slightly affects the GMV. The interaction between age and the polymorphism affected the left hippocampus volume, but this effect was not significant after FDR correction. We note that the current study enrolled non-demented elderly subjects, unlike the AD patients and unaffected siblings using in the aforementioned study. In addition, our results were based on the whole-brain analyses, while only the local regions of the GM were examined in that study. Further studies of larger samples and various ethnic populations are required to delineate the relationship of the rs1699102 polymorphism with brain atrophy during aging.

We are aware of several methodological limitations in this study. First, only the SNP rs1699102 but not other *SORL1* SNPs or haplotypes were singled out. The relatively very mild effect of the polymorphism on regional brain volume may in part be due to this selection. Second, the genetic effects on age-related cognitive decline and cortical GMV reduction identified in this study must be interpreted with caution due to the cross-sectional design of this study, which may result in a confounding effect because of the cohort effect. A prospective longitudinal study is needed to confirm these results. Third, the SorLA expression in the brain was not measured in this study, and this measurement may be necessary to clarify the exact mechanisms of the association between *SORL1* variants and age-related brain atrophy.

5. Conclusions

In conclusion, we observed the effects of the *SORL1* gene rs1699102 polymorphism on the age-related cognitive declines in episodic memory and processing speed, as well as a GMV reduction of the right MTP in a non-demented elderly Chinese Han population. Carriers of the rs1699102 T allele showed an accelerated age-related cognitive decline and GMV reduction compared with the CC group. These findings not only provide insight into how the *SORL1* variants shape the neural system to modulate cognitive decline but also support the hypothesis that *SORL1* may represent a candidate gene for late-onset AD.

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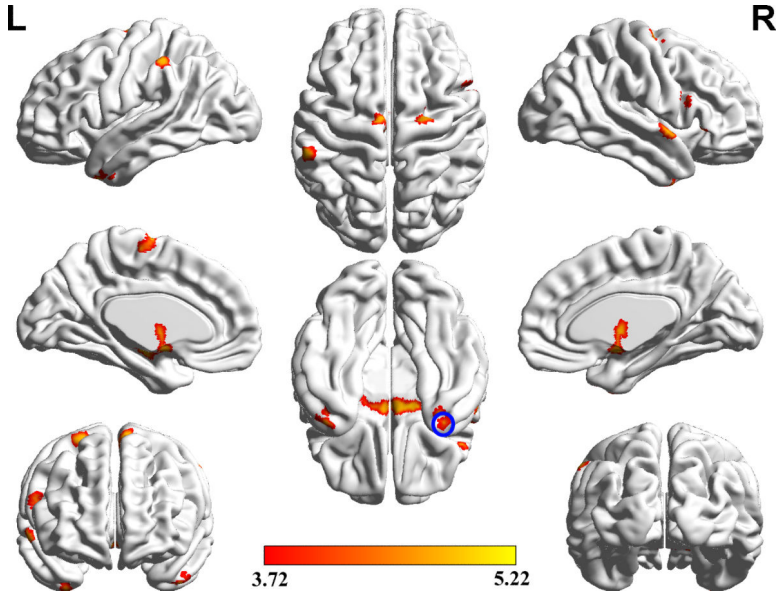

Figure 1.

Areas of GMV significantly affected by the interaction between genotypes and age without multiple comparison correction are presented, including the right middle temporal pole, left hippocampus, left middle temporal pole, right thalamus, right inferior frontal gyrus (pars opercularis), right middle temporal gyrus, left inferior parietal gyrus, right inferior frontal gyrus (pars orbitalis), right superior temporal pole, left supplementary motor area and right superior frontal gyrus. The area in the blue circle is the right middle temporal pole, which could withstand false discovery rate correction ($P < 0.05$).

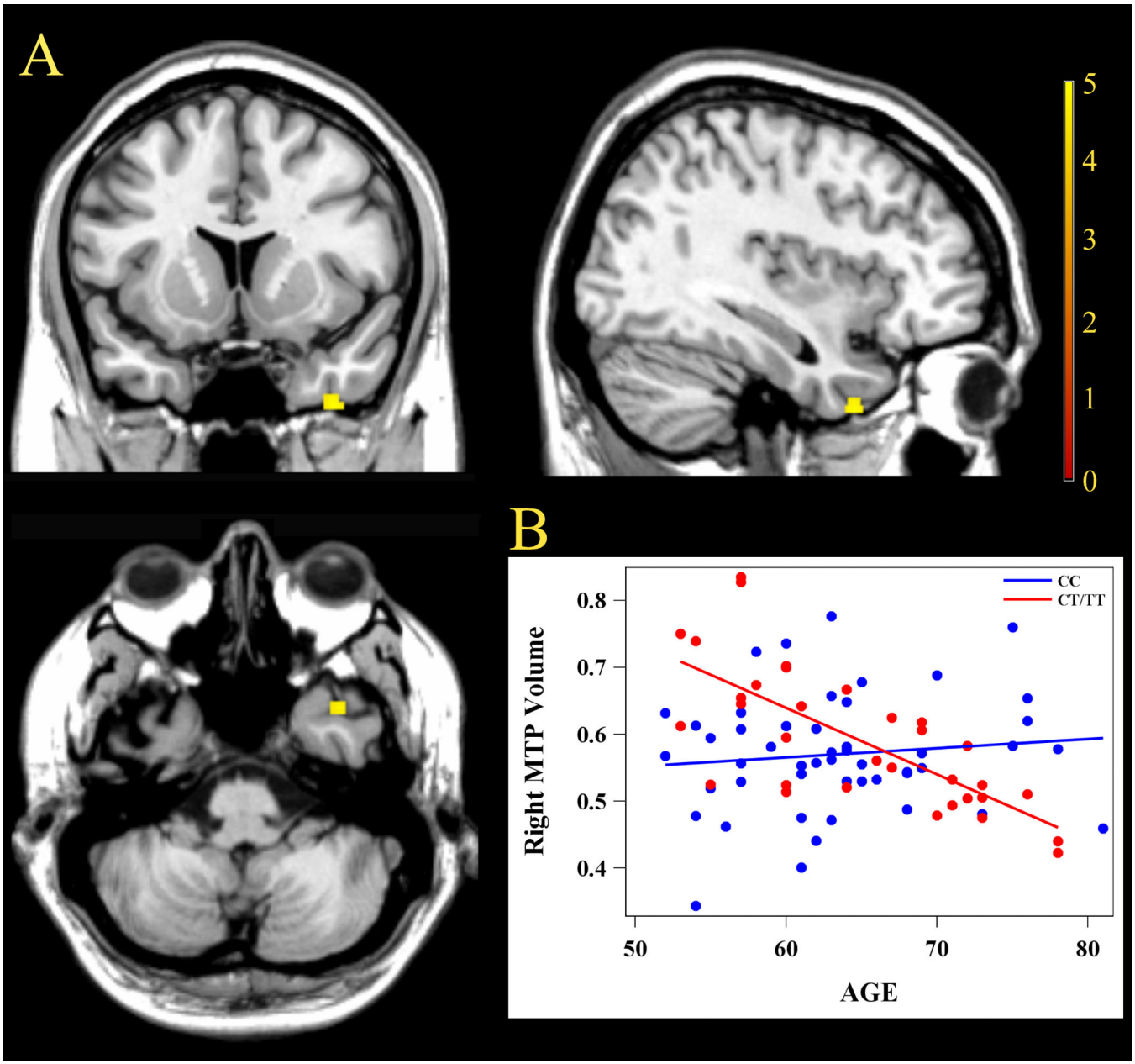

Figure 2.

Imaging graphic of the right middle temporal pole and slope changes of its gray matter volume with aging stratified by genotypes. (A) After false discovery rate correction ($P<$ 0.05), the right middle temporal pole retained a significant interaction effect with a cluster size of 63. (B) The significance of the interaction effect was reflected in the difference between the regression slopes of the two groups. Furthermore, the slope of the CT/TT group significantly differed from 0 ($F = 31.33$, $P< 0.001$), while the slope of the CC group did not ($F = 0.1$, $P = 0.758$).

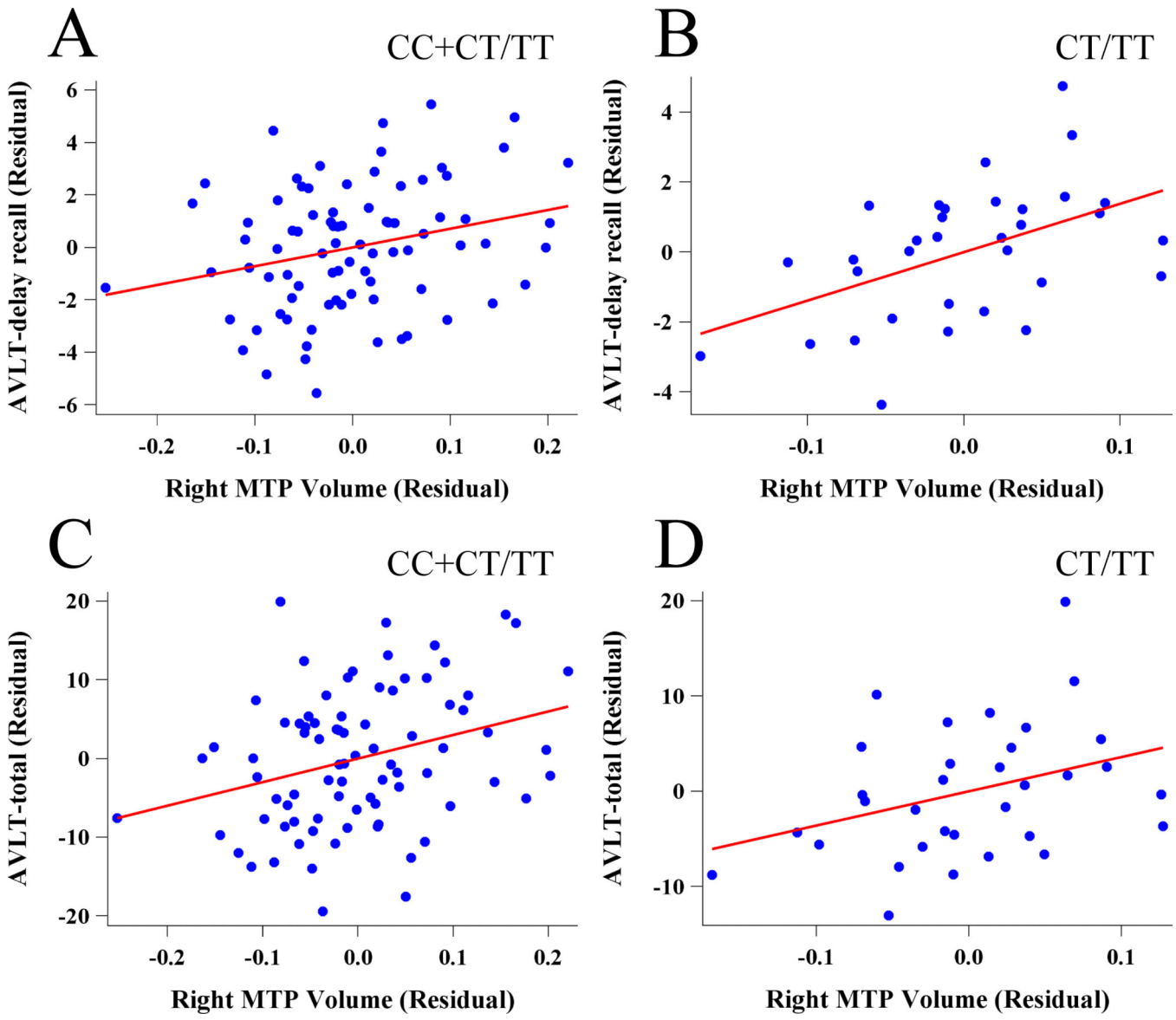

Figure 3.

Correlations between the neuropsychological tests and gray matter volume in the right middle temporal pole. (A) The right middle temporal pole volume positively correlated with the AVLT-delay recall in all subjects ($r = 0.25$, $P = 0.028$). (B) The right middle temporal pole volume positively correlated with the AVLT-delay recall in the CT/TT group ($r = 0.56$, $P = 0.002$). (C) The right middle temporal pole volume positively correlated with the AVLT-total in all subjects ($r = 0.30$, $P = 0.008$). (D) The right middle temporal pole volume tended to positively correlate with the AVLT-total in the CT/TT group ($r = 0.42$, $P = 0.023$). AVLT, Auditory Verbal Learning Test.

Table 1

Demographics and Neuropsychological Test Results of Subjects Based on *SORL1* Genotypes

	SNP ID	rs1699102	Main Group effect *p*-value*	Group × Age interaction *p*-value†
	CC (n=617)	CT/TT (n=163)		
Age, y (SD)	64.51(7.30)	65.35(7.23)	0.189	--
Gender, n (male/female)	221/396	68/95	0.165	--
Education, y (SD)	11.34(3.22)	11.44(3.28)	0.712	--
APOE ε4, n (carriers/noncarriers)	106/511	19/144	0.087	--
General mental status				
MMSE (SD)	27.94(1.62)	27.84(1.64)	0.454	0.417
Episodic memory				
AVLT-delay recall (SD)	5.84(2.53)	5.47(2.66)	0.164	0.026‡
AVLT-total (SD)	30.76(9.28)	29.76(9.37)	0.347	0.004‡
ROCF Recall (SD)	13.64(6.21)	13.13(6.69)	0.429	0.021‡
Spatial processing				
ROCF Copy (SD)	33.30(3.33)	33.55(3.04)	0.372	0.898
CDT (SD)	24.92(3.39)	24.33(4.26)	0.051	0.347
Language				
CVFT (SD)	45.07(8.50)	46.38(8.74)	0.056	0.098
BNT (SD)	23.25(3.54)	23.69(3.86)	0.188	0.980
Attention and processing speed				
SDMT (SD)	35.30(11.29)	35.37(11.11)	0.478	0.178
TMT-A time, s (SD)	58.35(20.20)	56.34(22.36)	0.156	0.015‡
Executive function				
TMT-B time, s (SD)	177.93(69.75)	169.97(64.43)	0.143	0.259
Stroop time, s (SD)	77.06(22.51)	76.66(23.73)	0.839	0.578

Abbreviations: MMSE, Mini-Mental State Examination; AVLT, Auditory Verbal Learning Test; ROCF, Rey-Osterrieth Complex Figure; CDT, Clock-Drawing Test; CVFT, Category Verbal Fluency Test; BNT, Boston Naming Test; SDMT, Symbol Digit Modalities Test; TMT, Trail Making Test; Stroop, Stroop Color-word Test; SD, standard deviation."--" indicates no data available.

*Comparisons between groups were performed by using the Pearson χ^2 test for gender and *APOE* ε4 and a two-sample t-test for age and education. An analysis of covariance (ANCOVA) was used to determine the main group differences in the neuropsychological test results with age, gender, education and *APOE* ε4 as covariates.

†GLM was used to determine the interaction between age and genotypes with age, group, group × age as predictor variables and gender, education, *APOE* ε4 as covariates.

‡$p< 0.05$.

Table 2

Areas of GMV Significantly Affected by the Interaction between Genotypes and Age

Location*	Cluster Size	*t*-value	*Z* value	MNI coordinates (mm)†		
				X	Y	Z
Middle Temporal Pole (R)	698	5.22	4.80	38	12	−47
Hippocampus (L)	265	5.12	4.72	−24	−15	−6
Middle Temporal Pole (L)	389	4.50	4.22	−45	15	−41
Thalamus (R)	675	4.23	4.00	12	−1	−9
Inferior Frontal Gyrus_pars opercularis (R)	194	4.21	3.98	57	15	25
Middle Temporal Gyrus (R)	143	4.16	3.93	60	−57	18
Inferior Parietal Gyrus (L)	145	4.02	3.81	−54	−33	43
Inferior Frontal Gyrus_pars orbitalis (R)	211	3.93	3.74	50	23	−6
Superior Temporal Pole (R)	123	3.85	3.66	63	3	−2
Supplementary Motor Area (L)	136	3.82	3.64	−5	−12	63
Superior Frontal Gyrus (R)	195	3.72	3.55	23	−7	66

Abbreviations: R, right; L, left.

*Areas with a cluster size exceeding 90 (the expected cluster size according to the SPM results) are displayed.

†The “X Y Z” denotes the coordinates of the primary peak locations in the MNI space.