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Apolipoprotein E ε4 Allele Is Associated with Reduced Retention of the "Where" Memory Component in Cognitively Intact Older Adults

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Abstract

Objective: The present study investigated the effect of the apolipoprotein E (ApoE) ε4 allele on the four memory components (i.e., *who*, *when*, *where*, and *what*) among cognitively intact older adults.
Methods: Participants comprised 47 cognitively intact older adults, who were classified into 2 groups based on the presence or absence of at least 1 ApoE ε4 allele. All participants completed standardized neuropsychological tests, including the Logical Memory subtest of the Wechsler Memory Scale-III with a revised scoring method.
Results: The results revealed that recollection for each component followed a pattern of who > what > when = where. Furthermore, a significant group-by-component-by-condition interaction indicated that the presence of the ApoE ε4 allele resulted in a disproportionately detrimental effect on the *where* component retention in the verbal episodic memory task; this finding was significantly correlated with hippocampal volumes.
Conclusion: These results highlighted the importance of evaluating the subcomponents of verbal episodic memory to detect subtle cognitive differences related to ApoE ε4 status, which could help elucidate the mechanism behind the cascades caused by ApoE ε4 in the trajectories of cognitive aging.

Keywords: Aging; Alzheimer's disease; Apolipoprotein E 4; Episodic memory; MRI

Age-related decline in episodic memory has been well documented (Alexander et al., 2012; Haaland, Price, & Larue, 2003; Tromp, Dufour, Lithfous, Pebayle, & Despres, 2015); however, great variability exists across individuals with regard to the extent of decline. The genotype of apolipoprotein E (ApoE), which is essential for normal lipid homeostasis in the brain (Bu, 2009) and has been identified as a genetic risk factor for developing Alzheimer's disease (AD) (Corder et al., 1993), has been demonstrated to show robust associations with normal-range variation in cognitive function (Wisdom, Callahan, & Hawkins, 2011), particularly memory and executive function, during late adulthood (McGue & Johnson, 2008; Small, Rosnick, Fratiglioni, & Backman, 2004). It was also demonstrated to affect the rate of cognitive decline in healthy elderly people (Salmon et al., 2013), with ApoE ε4 carriers showing faster decline over time compared with ε4 noncarriers.

The Logical Memory subtest of the Wechsler Memory Scale-Third Edition (WMS-III), a verbal story memory task, is one of the most commonly used tests for detecting AD in both clinical and research settings (Lange et al., 2002; Shi et al., 2014). However, the findings of previous studies on the effect of the ApoE ε4 allele on the performance of the story recall tasks were inconsistent. For instance, some studies have reported that cognitively intact older ApoE ε4 carriers performed more poorly in story recall (Honea, Vidoni, Harsha, & Burns, 2009; Levy et al., 2004; Samieri et al., 2014; Wilson et al., 2002), whereas others showed no significant difference (Jak, Houston, Nagel, Corey-Bloom, & Bondi, 2007; Lineweaver, Bondi, Galasko, & Salmon, 2014; Luciano et al., 2009) between the ε4 carriers versus noncarriers in nondemented older adults. The incompatible results of previous studies raise the question of whether the detrimental effects of the ApoE ε4 allele on story recall performance is too

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subtle to be detected consistently by the omnibus score used in a typical story recall test in older adults who are at high risk for developing AD.

Episodic memory involves recollections of various components of an event (Nairne, 2015; Tulving, 2002). These components consist of *when*, *where*, and *what* aspects (Tulving, 2002) that could represent memory for time, place, and location, respectively, and the contents of an episodic event. Although relevant studies are extremely rare, available evidence suggests that memory for various components may not be encoded or stored to the same extent during the memory process. For instance, previous studies concerning eyewitness memory have demonstrated different recollection performances for different components of episodic memory across groups, suggesting that the components can be separated (Dando, 2013; Sarwar, Allwood, & Innes-Ker, 2014; Yuille & Cutshall, 1986). A case study (Sirigu & Grafman, 1996) also demonstrated that a patient who experienced cerebral anoxia following heart failure showed selective amnesia for people (*who*) and dates (*when*) but not places (*where*) and content (*what*), associated with events. Additionally, Davis, Alea, and Bluck (2015) reported that, although no significant difference in the overall accuracy of recall for socially relevant stories between young and older groups was noted, there was an age-related difference in the components of recall accuracy of stories. Specifically, they discovered an age-related reduction of recall accuracy for gist information concerning the *why* component of the stories, and information concerning the *perceptual* and *emotional* or *thought* details of the stories.

Studies on the relationship between the differential recall of the various components of an episodic event and brain involvement are even fewer than behavioral studies. Some functional imaging studies have investigated the components of an episodic event in segregation using experimental tasks (e.g., object–location association tasks to investigate the *where* component, temporal order judgment tasks to investigate the *when* component, and object or scene recognition to investigate the *what* component). Those studies have identified an association between the lateral frontal and parietal regions with the memory of *where*; the lateral frontal, anterior cingulate gyrus, and parietal regions with the memory of *when*; and the lateral frontal regions with the memory of *what* information, in addition to common hippocampal activity in healthy young-to-middle-aged adults (Fujii et al., 2004; Kwok & Macaluso, 2015; Kwok, Shallice, & Macaluso, 2012; Nyberg et al., 1996). These studies have provided valuable evidence of the domain-specific memory processes in relation to brain involvement; however, the segregation approach used in these studies did not answer how the various memory components within one episodic event are related to the brain structure.

The role of the hippocampus as a convergence zone for binding various components of an episodic memory from distinct brain areas into an integrated representation, and for retaining newly acquired information and accessing stored information, has been well established (Alvarez & Squire, 1994; Backus, Bosch, Ekman, Grabovetsky, & Doeller, 2016; Ritchey, Wing, LaBar, & Cabeza, 2013) because of the rich reciprocal connections between the hippocampus and various cortical regions. A meta-analysis (Liu et al., 2015) revealed that the ApoE ε4 genotype is associated with neuropathological changes in the hippocampus in the AD spectrum population, including presymptomatic older adults. Although the mechanisms underlying the association of ApoE ε4 genotypes with hippocampal neuropathological changes are still to be determined, some evidence from cellular research and animal research has demonstrated that the ApoE ε4 genotype decreases the effectiveness of Aβ clearance and tau phosphorylation modulation in the hippocampus (Deane et al., 2008; Mahley, 1988; Ye et al., 2005). Despite clear evidence demonstrating the role of the hippocampus in episodic memory, whether the differential recall of components of an episodic memory can be observed and whether the integrity of the hippocampus can be associated with the recall of various components of an episodic memory if it was observed in populations such as older adults without dementia with the ApoE ε4 genotype remains uncertain. In addition, a link between the ApoE ε4 allele and regional changes in the frontal and parietal areas has also been reported (Seo, Choo, & Alzheimer's Disease Neuroimaging, 2016; Villemagne & Rowe, 2013; Wishart et al., 2006), although the specific regions involved have differed among studies and been inconsistent. Given that involvement of the frontal and parietal regions has been reported in the domain-specific memory process for the components in prior studies, the present study also explored the relationship between these brain regions and the recollection of memory components in relation to ApoE ε4 status.

Thus, in the present study, we revised the scoring method of the Logical Memory subtest of the WMS-III Manual and subdivided the details of the stories into four components (i.e., *who*, *when*, *where*, and *what*) to examine the effect of the ApoE genotype on the four components of episodic memory in cognitively unimpaired older adults. We hypothesized that individuals with the ApoE ε4 allele would demonstrate a disproportionate contribution to the four components in the learning and retention performances of verbal episodic memory tasks compared with the ε4 noncarriers and that such difference, if observed, would be associated with the integrity of the hippocampus given its role in binding information and the hypothetically compromised function of the hippocampal regions related to the ApoE ε4 allele. This study further explored the association between recall of memory components and the gray matter integrity of the lateral prefrontal and parietal regions.

Table 1. Demographic, clinical, and cognitive characteristics in the ApoE ε4+ and ε4− cognitively intact older groups

	ε4+	ε4−	
	$n = 24$ (mean, *SD*)	$n = 23$ (mean, *SD*)	*p* value
Demographic and clinical characteristics			
Age (years)	69.38 (4.30)	68.00 (4.97)	0.32
Education (years)	14.75 (2.17)	13.91 (3.14)	0.29
Sex (female/male)	15/9	13/10	0.68
History of hypertension (yes/no)	9/15	5/18	0.24
GDS	2.72 (3.00)	2.33 (2.21)	0.62
MMSE scores	28.58 (1.24)	29.10 (1.37)	0.20
Neuropsychological tests			
WAIS-3 Vocabulary (AcSS)	14.29 (2.07)	13.17 (2.69)	0.12
WAIS-3 Vocabulary (raw)	50.17 (8.12)	45.30 (11.36)	0.10
WAIS-3 Digit Span forward length (raw)	7.83 (1.30)	7.74 (1.13)	0.79
WMS-III LM-O immediate (AcSS)	14.42 (2.74)	14.61 (2.35)	0.80
WMS-III LM-O immediate (raw)	42.17 (9.39)	44.22 (8.43)	0.44
WMS-III LM-O delayed (AcSS)	13.96 (3.05)	14.65 (2.30)	0.39
WMS-III LM-O delayed (raw)	26.25 (9.10)	28.70 (6.29)	0.29
WMS-III LM-R immediate (raw)	39.39 (8.33)	41.95 (7.54)	0.28
WMS-III LM-R delayed (raw)	24.35 (8.13)	27.04 (5.06)	0.18
Color Trails Part 1 (sec)	46.25 (15.82)	40.43 (12.72)	0.17
Color Trails Part 2 (sec)	95.25 (30.40)	90.00 (28.72)	0.55

Note. AcSS = age-corrected scaled score; ApoE = apolipoprotein E; GDS = Geriatric Depression Scale; MMSE = Mini-Mental State Examination; SD = standard deviation; WAIS-3 = Wechsler Adult Intelligence Scale-III; WMS-III = Wechsler Memory Scale-Third Edition; LM = Logical Memory subtest; O = original scoring system; R = revised scoring system.

Materials and methods

Participants

A sample of 878 older adult participants, recruited from local communities during their attendance at a free yearly health examination for senior citizens in local hospitals between April 2014 and December 2017, completed the initial screening task (i.e., a Mini-Mental State Examination [MMSE;(Folstein, Folstein, & McHugh, 1975)]) to examine their cognitive statuses and ApoE genotypes (125 ApoE *ε2/ε3*; 610 ApoE *ε3/ε3*; 139 ApoE *ε3/ε4*; and 4 ApoE *ε4/ε4*) using DNA extracted from buccal swab samples. The protocol used for ApoE genotyping was described in detail in our previous study (Chang, Yen, Chen, Yan, & Tseng, 2016). Of these participants, 831 individuals were excluded from the present study because they did not meet the inclusion criteria ($n = 167$) described subsequently, or they did not respond to the invitation letter and phone calls or refused to participate in the following neuropsychological testing and structural magnetic resonance imaging sessions ($n = 664$). The final sample consisted of 47 cognitively intact older adult participants, who were right-handed, had a MMSE score $\geqq 26$, and had no history of brain injury, neurological disease, untreated hypothyroidism, psychiatric disorder, alcohol or drug abuse, or any severe hearing or vision impairment that might affect their neuropsychological performance. These participants were divided into two groups (i.e., ε4+, $n = 24$ with 2 ApoE *ε4/ε4*, and 22 ApoE *ε3/ε4*; ε4−, $n = 23$ with 20 ApoE *ε3/ε3* and 3 ApoE *ε2/ε3* cases) on the basis of the presence of at least one ApoE ε4 allele. Both the participants and researchers were blind to the participants' ApoE genotype status during the data collection period. Notably, information pertaining to the participants' history of hypertension was also collected given that evidence suggests that the ApoE ε4 genotype might be a risk factor contributing to hypertension (Shi et al., 2018; Stoumpos, Hamodrakas, Anthopoulos, & Bagos, 2013), and hypertension status may itself be associated with cognitive changes (Muela et al., 2017; Nguyen et al., 2016) and brain structure alterations (Beauchet et al., 2013). Demographic and clinical characteristics of the subgroups are presented in Table 1. The ethics committee and institutional review board at the University Hospital approved the study, and written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki.

Neuropsychological evaluation

A battery of neuropsychological tests (Table 1) was administered to all participants to assess cognitive abilities. The neuropsychological tests included the Vocabulary subtest and the Digit Span forward length of standardized Taiwanese versions of the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III) (Chen & Chen, 2002); the Logical Memory subtest of the

standardized Taiwanese version the WMS-III (Hua, Chang, Lin, Yang, Lu, & Chen, 2005); and the Color Trails Test Part 1 and Part 2 (D'Elia, Satz, Uchiyama, & White, 1996). Additionally, all participants completed the Geriatric Depression Scale (GDS) (Burke, Roccaforte, & Wengel, 1991).

The verbal episodic memory task

The material of this task followed the standardized testing procedure from the Logical Memory subtest of the WMS-III Manual, which consisted of two stories. Story A was read once to the participant, who then orally provided any information recalled. Story B was read twice to the participant, with any recalled information provided after each reading. The participant was asked to provide any information recalled from story A and then story B again after a 30-min delay. The examiner recorded the number of free recall units for all trials.

A revised scoring method, based on the concepts of previous studies (Power, 1979; Webster, Godlewski, Hanley, & Sowa, 1992), was developed in the present study because the original scoring system was not developed to segment the content of recall based on the four components of interest in the present study and because some of the content of recall was counted as two independent scoring units in the original scoring system (e.g., "at six o'clock in the afternoon" was counted as two scoring units [i.e., one of "at six o'clock" and the other as "in the afternoon"]), which we thought could be combined into one unit because of the conceptual proximity. Additionally, the original scoring system used an all-or-nothing scoring criterion for the individual items recalled, which may have compromised the measurement precision of the memory level underlying responses among individuals; consequently, half-point scoring was introduced for items, where applicable, in the revised system. Specifically, each recall unit provided by the participant was scored based on the following rules of the revised scoring system: (1) A full point credit (a score of 1) was scored if the detail description was consistent with the original story information; (2) a half-point credit (a score of 0.5) was scored if the response was not precise but consistent with the meaning of the original story detail; and (3) no credit (a score of 0) was scored if the participant provided incorrect information or did not provide the information from the original stories. A high inter-rater reliability of two licensed psychologists was established for the revised scoring criteria ($r = 0.973$) in the present study.

In addition, the content details of the stories were divided into four components—*who*, *when*, *where*, and *what*—based on Sirigu and Grafman (1996). The four components were described as follows: (1) *Who* details referred to information about names and titles of people (i.e., occupational titles); (2) *when* details included information about day of the week, time of day, events during a specific period of time, and specifics about when an event occurred; (3) *where* details referred to information about the location of an event, including the name of a city, district of a city, street, and building; and (4) *what* details referred to information about physical or emotional actions, action-related meaning, and reactions in others. Based on the revised scoring criteria, the highest possible accuracy score for story A was 22 (*who* = 6, *when* = 2, *where* = 6, *what* = 8), and the highest possible accuracy score for story B was 23 (*who* = 3, *when* = 4, *where* = 1, *what* = 15). The inter-rater reliability of three licensed psychologists for scoring the four components was high, with kappa ranging from 0.953 to 0.977. Additionally, the internal consistency, indicated by Cronbach's alphas, for the immediate ($\alpha = 0.818$) and delayed ($\alpha = 0.836$) recall conditions of the Logical Memory test using the revised scoring system were high. Although the individual component accuracy scores could be calculated for three learning trials (i.e., one from Story A and two from Story B) and the delayed recall trial of the two stories, we focused our component accuracy analyses on the immediate recall of Story A and the second reading of Story B, as well as the delayed recall of both stories.

In addition to the individual component accuracy scores (see Supplementary material online, *Table S1*), the ratio scores for each component in the immediate recall condition (learning ratio) and the delayed recall condition (retention ratio) were calculated. Specifically, the learning ratio was calculated by dividing the participant's scores for each component achieved on both Story A and the second reading of Story B by the maximum possible accuracy scores for each corresponding component in the two story trials combined during the immediate recall condition. The retention ratio was calculated by dividing the participant's score for each component during the delayed condition by the participant's corresponding component score from the immediate condition.

Structural magnetic resonance imaging data acquisition and processing

All participants were scanned using a 3-tesla magnetic resonance imaging system (Magnetom Trio; Siemens, Erlangen, Germany) with a 32-channel phased-array head coil. T1-weighted structural brain images were acquired using a three-dimensional (3D) magnetization prepared rapid gradient echo sequence (coronal slicing; repetition time = 2000 ms; echo time = 2.98 ms; flip angle = 9; field of view = 256 × 192 × 208 mm^3; matrix size = 256 × 192 × 208 mm^3; voxel size = 1 × 1 × 1 mm^3).

The present study used the FreeSurfer analysis suite (Version 5.1.0; Martinos Center for Biomedical Imaging, Charlestown, MA) for quality review, registering, and processing of data. The processing included volumetric and subcortical segmentation, thickness measurement of cortical surface reconstruction, and parcellation into distinct regions of interest (ROIs). Data were visually inspected, and manual interventions were performed when the automated steps failed quality assurance review, particularly for the subcortical segmentation. The analyses were confined to ROIs relevant to the present study and based on a literature review. Specifically, the ROIs included the volumetric measures of the bilateral hippocampi, and thickness measures of the bilateral dorsolateral prefrontal (comprising the superior frontal, caudal middle frontal, and rostral middle frontal regions) and lateral parietal (comprising the superior parietal and inferior parietal regions) regions. Because specific hypotheses for hemispheric effects were not proposed in the present study, the left and right ROIs for the three corresponding brain variables were collapsed to reduce the number of comparisons.

Statistical analysis

Univariate analyses of variance (ANOVAs) and chi-square (i.e., sex and number of people with a history of hypertension) tests were conducted to examine group variations in demographics, clinical characteristics, and neuropsychological performance. The alpha level of statistical significance was set at 0.05 for the analysis of demographic and clinical characteristic (i.e., age, education, sex, history of hypertension, GDS score, and MMSE score) variables, whereas the alpha level was set at 0.0045 (Bonferroni correction) for analyses of the neuropsychological tests.

To determine group variations in learning and retention ratios among the four components in the verbal episodic memory task, a group × components × test condition (2 × 4 × 2) three-way mixed ANOVA was conducted, in which the group variable ($\varepsilon4+$, $\varepsilon4-$) was entered as the between-subject variable, and the four components (*who*, *when*, *where*, and *what*) and the two test conditions (learning ratio and retention ratio) were entered as the within-subject variables. The Greenhouse–Geisser correction was applied whereas the assumption of sphericity in repeated-measure ANOVAs was violated. Independent or paired sample *t* tests, or ANOVAs, were performed for post hoc pairwise comparisons; in cases where the assumption for homogeneity of variance was violated, the statistical results of unequal variances were reported. The alpha level of statistical significance was set at 0.05 for the main and interaction effects. A Bonferroni adjustment Type I error rate of 0.0083 was applied for the post hoc analyses of the memory components. A Bonferroni correction was also applied for the post hoc analyses of the behavioral interaction effects (Kirk, 2013), using the per-family error rate (α_{PF}) divided by the number of comparisons (c) as the significance threshold ($\alpha = \alpha_{PF}/c$, i.e., 0.019).

For assessing group differences in the three morphometric variables (i.e., hippocampus, dorsolateral prefrontal, and lateral parietal regions), the effect of sex was first regressed out for all the three ROI measures. Hippocampal volume was further corrected for individual differences in head size by regressing out the effect of estimated total intracranial volume (Buckner et al., 2004). The standardized residual values (z-scores) of the three ROIs were used for further statistical analysis. The volumes and cortical thickness variables were averaged across both hemispheres values. Independent *t* tests were computed to assess gray matter integrity of the three ROIs between groups, and a Bonferroni correction Type I error rate of 0.0167 was applied. Effect sizes (Cohen's *d*) were calculated for the cognitive and brain variables that reached significance. Spearman's rank order correlations were conducted to assess the association between the measures of the effect related to the ApoE $\varepsilon4$ allele on the verbal episodic memory task and brain variables. Because of the exploratory nature of the analysis, a conventional alpha level of 0.05 was applied. Furthermore, a moderation analysis was performed using PROCESS v3.3 macro for SPSS, Model 1 (Hayes, 2013, 2018), to investigate a possible moderation role of the ApoE $\varepsilon4$ allele between the relationship of the brain variables and memory performance, which reached significance during the correlation analyses. The scores on each predictor variable (i.e., brain variables and ApoE $\varepsilon4$ allele) were mean centered prior to the analysis. The two predictors and their interaction term (i.e., brain variables × ApoE $\varepsilon4$ allele) were entered into a simultaneous regression model to examine the main effects and moderating effect of the ApoE $\varepsilon4$ allele on the relationship between brain morphometry and memory performance, respectively. If the interaction variable was significant and the moderator hypothesis was supported (Baron and Kenny, 1986), then a simple slope analysis of the Johnson–Neyman method within the PROCESS macro was conducted to examine the moderator values for the ApoE $\varepsilon4$ status that reach significance. The bootstrapped 95% confidence intervals (CI) in 5,000 resamples were used in this study. All statistical analyses were conducted using IBM SPSS (Version 21.0) for Windows (IBM Corp., Armonk, New York).

Results

Demographic, clinical, and neuropsychological data between groups

Table 1 shows the demographic and clinical characteristics for the two groups. The two groups did not differ in age, education, sex distribution, frequency distribution of hypertension, and MMSE and GDS scores (all p values > 0.05). Regarding neuropsy-

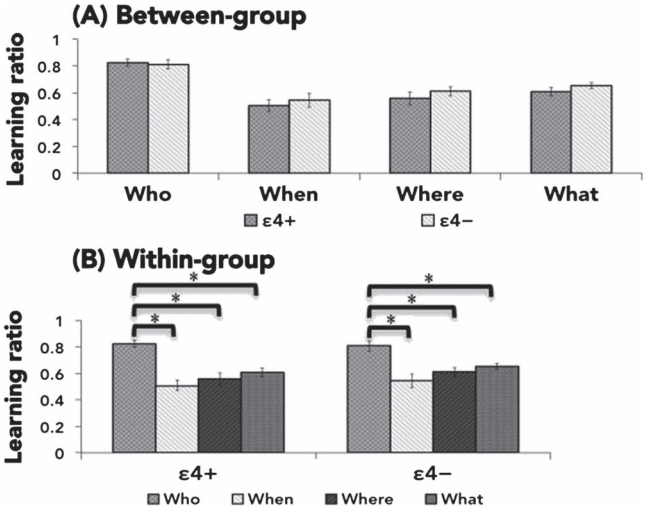

Fig. 1. Between-group (**A**) and within-group (**B**) learning ratios of the four components (i.e., *who*, *when*, *where*, and *what*) in the verbal episodic memory task. Error bars denote the standard error. ∗Significant group difference at $p < 0.019$.

chological test performances (Table 1), the two groups did not show significant differences on the Vocabulary subtest, Digit Span forward length, Color Trails Test Part 1 or Part 2, or the immediate and delayed total accuracy scores of the Logical Memory subtest using either the original standardized scoring system in the Manual or the revised scoring system (all p values > 0.0045).

Performances in the four components of the verbal episodic memory task

The main purpose of this study was to examine whether the two groups exhibited differential memory performance on the four components; therefore, the analyses focused on investigating the main effect for components as well as group-by-component and group-by-component-by-condition interaction effects. The results revealed a significant main effect for components ($F_{(2.14, 96.58)} = 19.92$, $p < 0.001$, $\eta_p^2 = 0.31$). The post hoc analyses following the main effect of components showed a significantly higher performance of the *who* component than in the *when* ($t_{(46)} = 5.96$, $p < 0.001$, Cohen's $d = 1.09$), *where* ($t_{(46)} = 5.33$, $p < 0.001$, Cohen's $d = 0.83$), and *what* ($t_{(46)} = 3.52$, $p = 0.001$, Cohen's $d = 0.51$) components. Recollection of the *what* component was significantly higher than that of the *when* ($t_{(46)} = -4.28$, $p < 0.001$, Cohen's $d = 0.83$) and *where* ($t_{(46)} = -3.06$, $p = 0.004$, Cohen's $d = 0.53$) components. The *when* component was comparable to the *where* component ($t_{(46)} = -1.91$, $p = 0.062$). Overall, the recollection for each component showed a pattern of *who* > *what* > *when* = *where*.

A significant group-by-component interaction effect was observed ($F_{(2.14, 96.58)} = 3.16$, $p = 0.043$, $\eta_p^2 = 0.07$), with the $\varepsilon 4+$ group displaying poorer performance in the *where* component ($F_{(1, 141.58)} = 8.24$, $p = 0.004$, $\eta_p^2 = 0.06$) but not in the other components (all $p > 0.019$) compared with the performance of the $\varepsilon 4-$ group. Furthermore, a significant three-way group-by-component-by-condition interaction effect ($F_{(2.41, 108.85)} = 3.26$, $p = 0.033$, $\eta_p^2 = 0.07$) was observed. The post hoc analyses revealed that, under the immediate recall condition, no significant difference existed in the learning ratio of the *who* ($F_{(1, 295.43)} = 0.03$, $p = 0.852$), *when* ($F_{(1, 295.43)} = 0.31$, $p = 0.578$), *where* ($F_{(1, 295.43)} = 0.54$, $p = 0.463$), or *what* ($F_{(1, 295.43)} = 0.40$, $p = 0.529$) components between groups (Fig. 1A). However, the $\varepsilon 4+$ group demonstrated a lower retention ratio in the *where* component ($F_{(1, 295.43)} = 15.11$, $p < 0.001$, $\eta_p^2 = 0.05$) but comparable performance to the $\varepsilon 4-$ group in the *who* ($F_{(1, 295.43)} = 1.28$, $p = 0.259$), *when* ($F_{(1, 295.43)} = 0.10$, $p = 0.753$), and *what* ($F_{(1, 295.43)} = 0.02$, $p = 0.875$) components (Fig. 2A).

We further examined the differences among the four memory components within each group for learning and retention ratios. For the learning ratio, the results revealed that both groups demonstrated the same pattern of performance levels for the four components. The four memory components were not uniformly encoded within either the $\varepsilon 4+$ ($F_{(3, 205.43)} = 9.19$, $p < 0.001$, $\eta_p^2 = 0.12$) or the $\varepsilon 4-$ ($F_{(3, 205.43)} = 5.69$, $p < 0.001$, $\eta_p^2 = 0.08$) group. Specifically, in the $\varepsilon 4+$ group, the learning ratio of the *who* component was significantly higher compared with that of the *when* ($t_{(23)} = 6.88$, $p < 0.001$, Cohen's $d = 1.75$), *where* ($t_{(23)} = 7.02$, $p < 0.001$, Cohen's $d = 1.43$), and *what* ($t_{(23)} = 8.17$, $p < 0.001$, Cohen's $d = 1.49$) components. Similarly, in the $\varepsilon 4-$ group, the learning ratio of the *who* component was significantly higher than that of the *when* ($t_{(22)} = 4.35$, $p < 0.001$, Cohen's $d = 1.28$), *where* ($t_{(22)} = 4.88$, $p < 0.001$, Cohen's $d = 1.23$), and *what* ($t_{(22)} = 5.50$, $p < 0.001$, Cohen's $d = 1.15$) components (Fig. 1B).

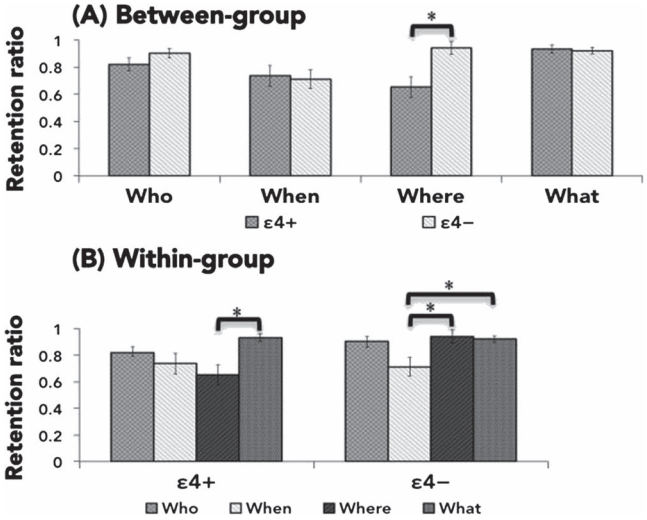

Fig. 2. Between-group (A) and within-group (B) retention ratios of the four components (i.e., *who*, *when*, *where*, and *what*) in the verbal episodic memory task. Error bars denote the standard error. ∗Significant group difference at $p < 0.019$.

Table 2. Raw mean volumes of hippocampus, and cortical thickness of dorsolateral, prefrontal, and lateral parietal regions in the ApoE ε4+ and ε4− cognitively intact older groups

	ε4+	ε4−	
	$n = 24$ (mean, *SD*)	$n = 23$ (mean, *SD*)	*p* value
Gray matter measures			
Hippocampus (mm^3)	3729.19 (411.03)	3747.92 (335.35)	0.67
Dorsolateral prefrontal (mm)	2.56 (0.11)	2.55 (0.07)	0.87
Superior frontal (mm)	2.76 (0.14)	2.76 (0.09)	0.80
Caudal middle frontal (mm)	2.59 (0.10)	2.56 (0.08)	0.48
Rostral middle frontal (mm)	2.34 (0.11)	2.33 (0.08)	0.99
Lateral parietal (mm)	2.38 (0.13)	2.35 (0.09)	0.54
Superior parietal (mm)	2.27 (0.13)	2.21 (0.08)	0.14
Inferior parietal (mm)	2.50 (0.15)	2.50 (0.11)	0.73

Note. ApoE = apolipoprotein E; Statistical comparison of the brain variables (i.e., volumetric measurements of the hippocampus and cortical thickness measurements of the dorsolateral, prefrontal, and lateral parietal regions) was based on standardized *z*-scores after controlling for the effects of sex. The hippocampal volume was also corrected for differences in head size by regressing out the estimated total intracranial volume.

By contrast, the retention ratios of the four components differed within the ε4+ group ($F_{(3,\ 205.43)} = 6.56$, $p < 0.001$, $\eta_p^2 = 0.09$) versus the ε4− ($F_{(3,\ 205.43)} = 4.90$, $p = 0.002$, $\eta_p^2 = 0.07$) group. Specifically, in the ε4+ group, the retention ratio of the *where* component was significantly lower than that of the *what* ($t_{(23)} = -3.50$, $p = 0.002$, Cohen's $d = 0.98$) component. In the ε4− group, the retention ratio of the *when* component was significantly lower compared with that of the *where* ($t_{(22)} = -2.84$, $p = 0.009$, Cohen's $d = 0.79$) and *what* ($t_{(22)} = -2.62$, $p = 0.015$, Cohen's $d = 0.82$) components (Fig. 2B).

Brain morphometry between groups and its relationship with episodic memory measures

The results of the independent *t* test revealed that the two groups did not differ in the gray matter integrity of the hippocampal ($t_{(40)} = 0.43$, $p = 0.670$), dorsolateral prefrontal ($t_{(40)} = -0.15$, $p = 0.879$), and lateral parietal ($t_{(40)} = -0.62$, $p = 0.542$) regions. The raw mean volume of the hippocampus and the thicknesses of the dorsolateral prefrontal and lateral parietal regions are presented in Table 2.

Because the group difference in the ApoE ε4 allele was noted mainly for the *where* component in the retention condition, the following correlational analyses were restricted to examining the relationship between the *where* component of the retention condition and the three brain variables for the full cohort. The results revealed that the hippocampal volume ($r_s = 0.30$, $p = 0.024$), but not the thicknesses of the dorsolateral prefrontal ($r_s = -0.08$, $p = 0.307$) or parietal ($r_s = 0.001$, $p = 0.497$) regions, was significantly correlated with the *where* component of the retention condition. A moderation analysis was further conducted

to investigate a possible moderation role of the ApoE ε4 allele to the association between the hippocampal volume with the *where* component of the retention condition. No significant main effect for the hippocampal volume (beta = 0.07, 95% CI = −0.03, 0.19; $p = 0.181$) was revealed, but a significant main effect for the ApoE ε4 allele status (beta = −0.28, 95% CI = −0.49, −0.08; $p = 0.007$) was observed. Furthermore, the interaction effect between hippocampal volume and the ApoE ε4 allele status was not significant (beta = −0.03, 95% CI = −0.26, 0.19; $p = 0.752$), indicating that the relationship between hippocampal integrity and the *where* component of the retention condition was not moderated by the ApoE ε4 allele status.

Discussion

The present study investigated the potential effects of the ApoE ε4 allele on four memory components (i.e., *who*, *when*, *where*, and *what*) in the learning and retention conditions among cognitively intact older adults. We further examined the association of the gray matter integrity in the hippocampal, prefrontal, and parietal regions with the memory recall of the components related to the ApoE ε4 allele. The results revealed that the presence of at least one ApoE ε4 allele had a disproportionately detrimental effect on memory retention in the *where* component during a verbal episodic memory task, and such an effect was associated with the hippocampal volume.

As expected, we found that the four memory components were not uniformly encoded in the older adults' memory systems regardless of their ApoE status, which was consistent with studies concerning eyewitness memory (Davis et al., 2015; Sarwar et al., 2014; Yuille & Cutshall, 1986), but inconsistent with memory theories that have postulated that all components of an episodic event are evenly encoded and holistically recollected (Eichenbaum, Sauvage, Fortin, Komorowski, & Lipton, 2012; Horner, Bisby, Bush, Lin, & Burgess, 2015; Moscovitch, Cabeza, Winocur, & Nadel, 2016). In the present study, the results revealed that the recollection for the stories followed a pattern of who > what> when = where. These results may be explained by a general aging effect with increased vulnerability of temporal and spatial context information (Bastin, Van der Linden, Michel, & Friedman, 2004; Chalfonte & Johnson, 1996; Rajah, Languay, & Valiquette, 2010). Alternatively, because the four components were not distributed evenly among the beginning, middle, and end positions (see Supplementary material online, *Table S2*), it raises a question as to whether the serial position effect (Atkinson & Shiffrin, 1968) might explain the poorer memory for the *when* and *where* components relative to other components. In our test stimuli, the *when* component appeared more frequently in the middle than at the beginning or end positions of the stories; the *where* component appeared more frequently at the beginning than at other positions; the *who* component was distributed more at the beginning and end positions of the stories as opposed to the middle; the *what* component was distributed more at the middle and end than at the beginning positions of the stories. If the serial position effect played a role in explaining our findings of poor memory for *when* and *where* components, it suggests a relatively stronger recency effect but an unobvious primacy effect for story recall concerning the ApoE status. In contrast to our findings, Miller and colleagues (Miller et al., 1977) reported that both marijuana and placebo groups demonstrated a strong primacy effect and an unobvious recency effect with prose materials, whereas another research team (Bower & Clark, 1969) indicated no significant serial position effect for narrative recall. The discrepancy among studies raised an empirical question of how the serial position curve for story or prose recall may differ from that of word lists. Future studies with a more sophisticated experimental design and manipulation of study materials are essential to disentangling the discrepancies in the literature.

In addition, studies have reported that older adults may depend more on gist memory (i.e., information for an abstracted and semantically rich representation) relative to detailed memory (i.e., the specific verbatim information) of a story (Reder, Wible, & Martin, 1986), which may be related to a limited attentional capacity (Hudon et al., 2006). In contrast to our findings with poorer recollection for both the *when* and *where* components, previous studies have revealed a trend of lower recollection for the *when* component compared with other components in older individuals using autobiographical or nonautobiographical events (Crawley & Pring, 2000; Davis et al., 2015; Wagenaar, 1986), which suggested that the *who*, *where*, and *what* components are essential information, whereas the *when* component is noncanonical information (Davis et al., 2015; Wagenaar, 1986) and typically does not retain in memory with a precise label (Friedman, 1993). Although parts of our results (i.e., poor *when* recollection) were consistent with previous studies on gist memory, our findings concerning the *where* component could not be explained by the gist memory effect.

In support of our hypothesis, we demonstrated that the ApoE ε4 allele exerted a disproportionate memory decay only for the *where* component, and this could not be explained by the serial position or gist memory effect mentioned here because we did not observe a similar pattern of memory decay for the *when* component. Such finding was also consistent with previous findings suggesting that the detrimental effect of the ApoE ε4 allele on memory in general was mainly observed in the retention phase rather than in the learning phase (Levy et al., 2004; Mormino et al., 2014). Although impairments of visuospatial ability have been identified as an early diagnostic sign of preclinical AD and mild cognitive impairment (Johnson, Storandt, Morris, & Galvin, 2009; Papp, Snyder, Maruff, Bartkowiak, & Pietrzak, 2011), the detrimental effect on the *where* component in the present study was obtained through a verbal episodic memory task rather than from tasks that measured visuospatial memory

directly. Martin and colleagues (Martin, Meador, Loring, Bowers, & Heilman, 1990) suggested that the impact of verbal codes was crucial in the early learning stage, which affected the adequacy of retaining and organizing the information of spatial context over time. Indeed, previous studies have found that AD patients have difficulty in retrieving mental images generated during the encoding stage (Hussey, Smolinsky, Piryatinsky, Budson, & Ally, 2012). Poor retention of auditorily presented verbal information, especially for the spatial component observed in the presymptomatic ApoE ε4 carriers of the present study, possibly resulted from changes in the ability to form mental representations of spatial information.

The lack of significant differences in the gray matter measures of our ε4+ samples—particularly in the hippocampal structures—compared with those of the ε4− group was unexpected and inconsistent with our hypotheses. A possible explanation for this unexpected result is that the relatively small sample size in this study reduced the power to detect differences related to the structural imaging. Our samples were also possibly relatively homogeneous because we employed thorough screening before enrolling participants in the study; the two groups were also similar in aspects of demographic variables, frequency distribution of hypertension, and mood status, which might have resulted in more biologically homogeneous samples. Despite that, a significant association between the ApoE ε4 allele–related decrease in memory retention for the *where* component and smaller hippocampal volumes was observed. Such findings indicated that, although structural changes in the hippocampus related to the ApoE ε4 allele may have been too subtle for detection by structural brain imaging at a group level, disruptions of the hippocampal function, which is binding and consolidates the memory of various components of an episodic event (Alvarez & Squire, 1994; Moscovitch et al., 2005), may have already been underway in the ε4 carriers. Such changes were detectable through a refined memory measurement. Notably, our findings did not support the moderating role of the ApoE ε4 genotype on the association between the hippocampal volume and the *where* memory retention. Although unexpected, such results are consistent with a recent study (Wang et al., 2019) that observed a deleterious effect of ApoE ε4 on the delayed recall of a word-list verbal memory test that varied by the degree of hippocampal atrophy among the MCI patients, particularly those with small-to-moderate hippocampal atrophy. In contrast, the interaction effect of ApoE ε4 and hippocampal integrity on memory was absent for the cognitively intact old adults. In our study, all the participants were cognitively intact older adults, and it is possible that the integrity of the hippocampus in these participants has not exceeded the threshold where the moderator effect can be observed on the basis of Wang and colleagues' findings. Therefore, it will be interesting to extend our study sample to MCI patients and to further examine the moderator effect of ApoE ε4 status in the future.

Other factors, such as level of Aβ burden or neural compensatory mechanism, may complicate the link between ApoE ε4 genotypes and hippocampal volumetric measurement in the presymptomatic stage, which is beyond the scope of this study but certainly warrants further investigation. Future studies using functional brain imaging should also provide more insight into the relationship between hippocampal integrity and recall of memory components.

The present study also explored the association between the integrity of the prefrontal and parietal regions and the observed ApoE ε4 allele–related susceptibility of information retention related to *where*. The findings of no correlations were inconsistent with prior studies using functional brain imaging (Fujii et al., 2004; Kwok & Macaluso, 2015; Kwok et al., 2012; Nyberg et al., 1996); these studies had identified a frontal–parietal network in relation to *where* information retrieval through visuospatial memory task paradigms. This may be explained by the methodological differences of the task paradigms used considering the *where* component in the present study was measured through a verbal episodic memory task rather than a conventional visuospatial memory task. In addition, the literature was inconclusive on the ApoE ε4 genotype–related regional changes in the frontal and parietal areas, and evidence suggests that factors such as comorbid vascular risk factors (e.g., hypertension) may interact with the ApoE ε4 genotype to jointly, rather than the ApoE ε4 genotype per se, contribute to the alternations of brain structure integrity in these brain regions (Wang et al., 2015; Williams et al., 2019). Consequently, it is possible that a significant correlation between the frontoparietal structure integrity and memory performance of the *where* component may emerge for hypertensive ε4+ individuals. The insufficient sample size of hypertensive individuals in the present study precluded us from testing such a hypothesis, but preliminary post hoc correlational analyses supported our speculation because we observed significantly positive correlations between the variables of the frontal and parietal regions and the *where* component retention ratios within the hypertensive ε4+ individuals ($r_s = 0.70$, $p = .027$ for the frontal variable; $r_s = 0.84$, $p = .004$ for the parietal variable). Because our study is the first to report such memory patterns related to the ApoE ε4 genotype and no clear parallels in the published literature exist, further studies investigating the relationship of brain–memory components are warranted.

To the best of our knowledge, the present study was the first to investigate the specificity of the four components in the context of episodic memory and relate that to the ApoE ε4 status in cognitively normal older adults. The findings revealed that ApoE ε4 status affected verbal memory only when we separated the four memory components, but not when we combined them into an omnibus score, which indicated the value of evaluating different components in verbal episodic memory as it could help detect subtle cognitive differences constituted of cognitive phenotypes related to the ApoE genotype. Nevertheless, some methodological limitations of our study should be noted. First, the highest possible scores for each component were not equal within a story, given that we did not attempt to modify the standardized test stimuli. Despite that, Sirigu and Grafman (1996)

found that their results for a selective amnesia case were similar, either with or without increasing the maximum possible scores for individual memory components, which could provide evidence to support the robustness of our findings in the present study. Second, our sample size was relatively small, which might have reduced the generalizability of the findings and precluded us from examining a possible ApoE ε4 gene dose effect and the potential protective role of the ApoE *ε2* gene. Notably, we conducted power analyses of our findings, which revealed an adequate power of 0.99 according to the estimated power curve for the current sample size and a medium-to-large effect size regarding the cognitive effects. Furthermore, the present study adopted a cross-sectional design; thus, our ability to predict how the cognitive phenotypes observed may contribute to various cognitive aging trajectories longitudinally was limited.

The current study revealed that the four components of the verbal episodic memory task were differentially encoded and retained in older adults' episodic memory systems, and ApoE ε4 carriers were particularly susceptible to information retention related to *where*. Such a finding underscores the importance of taking into account the relative performances among different components of the verbal episodic memory measures, rather than relying on an overall score that is currently used in research and clinical practice. Although the differences between the cognitive phenotypes associated with the ApoE genotype may be subtle, identifying which specific aspects of cognitive functioning are affected could help elucidate the mechanism behind the cascades caused by ApoE ε4 in the trajectories of cognitive aging.

Supplementary Data

Supplementary material is available at *Archives of Clinical Neuropsychology* online.

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Conflict of Interest

None declared.

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