國立臺灣大學理學院心理學研究所

碩士論文

Graduate Institute of Psychology

College of Science

National Taiwan University

Master Thesis

輕度認知功能障礙患者的語文連結記憶

Verbal Associative Memory in Individuals with Mild Cognitive Impairment

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中華民國 104 年 1 月

January, 2015

摘要

過去西方研究發現輕度認知功能障礙患者與早期阿茲海默氏症患者皆有較差的連結記憶。本研究依中文字特性產生不同種類的字對，以了解中文使用者裡輕度認知功能障礙患者的語文連結記憶表現，並嘗試修改現有臨床工具，比較不同版本的差異。研究發現輕度認知功能障礙組的連結記憶表現明顯較差，於延宕再認階段有較多語意相關、字形相關、與重組的錯誤再認，且與左側海馬迴體積有顯著地相關。與過去研究一致發現輕度認知功能障礙患者有較差的連結記憶，其中輕度認知功能患者具有較多的語意相關錯誤，暗示阿茲海默氏症前驅期的語意處理功能退化。

關鍵詞：連結記憶、中文字對學習、輕度認知障礙、阿茲海默氏症、字詞配對測驗

Verbal Associative Memory in Individuals with Mild Cognitive Impairment

Pei-Ching Chen

Abstract

Background: Previous studies have demonstrated individuals with mild cognitive impairment (MCI) and early Alzheimer's disease (AD) were defective in associative memory performances compared to healthy controls (HC). However, it remains unclear how verbal associative memory is affected in Chinese speakers with MCI, given the unique features of the Chinese language as oppose to the alphabetic language.

Objective: The study aimed to examine verbal paired memory in Chinese speakers with MCI compared to normal aging.

Methods: Twenty-two MCI and 25 age- and education-matched HC participated in the study. All participants underwent a comprehensive neuropsychological battery, a word association task, and a modified recognition test of Verbal Paired Associate subtest of the Wechsler Memory Scale -Third Edition (Verbal PA of the WMS-III). In addition, they underwent a structural magnetic resonance imaging.

Results: The results showed that the MCI group had worse associative memory

compared to the HC group even after controlling performance of item memory. During the delayed associative recognition, the MCI group committed more semantically-related, orthographically-related, and rearranged type false alarms compared to the HC group. The scores of associative memory were also significantly correlated with left hippocampus volume. In addition, performance on the modified recognition of Verbal PA of the WMS-III versus the original version was found significantly different.

Conclusion: These results are in line with studies that showed associative memory impairment in individuals with MCI. The high number of semantically-related false alarms found in individuals with MCI suggests possible early disruptions in semantic processing in prodromal AD.

Keywords: associative memory, verbal paired learning, Mild Cognitive Impairment, Alzheimer's disease, Chinese character

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1. Introduction

1.1. Alzheimer's disease and Mild Cognitive Impairment

Dementia of Alzheimer type is known as the most common neurodegenerative dementia type, and it gradually causes individuals unable to live independently. The initial symptom reported is usually memory function decline with insidious onset and gradual progression; poor judgment, word-finding difficulty, apraxia, and poor personal hygiene come up subsequently along with disease progression (Terry & Davies, 1980). Previous studies have demonstrated that the earliest decline function in AD is anterograde episodic memory, which is characterized by consolidation impairment; retrograde episodic memory deficit with temporally graded is also common. In addition, the onset of executive dysfunction, such as difficulty in inhibition, information manipulation, and attention, are regarded as parallel with memory decline (see review Storey, Kinsella, & Slavin, 2001).

According to Braak & Braak stages of AD pathology, intracellular neurofibrillary changes are first observed in entorhinal and transentorhinal regions of the medial temporal lobe, followed by the hippocampal regions involvement, and then the isocortex is involved in the end stage (Braak & Braak, 1991). The evolution of neuropathological and brain structure changes is associated with clinical symptoms of individuals with AD (Arriagada, Growdon, Hedley-Whyte, & Hyman, 1992; Deweer

et al., 1995; Köhler et al., 1998). Therefore, it is probable to identify high risk population who may develop AD based on cognitive function evaluation and neuropathological-related changes in brain.

Mild Cognitive Impairment (MCI) with intermediate level of cognitive function between normal aging and dementia has been considered a high risk population converting to dementia (Petersen et al., 2001). After the first MCI diagnostic criteria and subtypes were proposed (Petersen, 2004; Petersen et al., 1999), researchers have dedicated to study the characteristic of MCI. Among these subtypes, amnestic-MCI (a-MCI) has been recognized as prodromal AD because their memory impairment and the pattern of brain morphometric changes are similar to AD (Chetelat et al., 2002; Kordower et al., 2001; Perri, Carlesimo, Serra, Caltagirone, & Early Diagnosis Group of the Italian Interdisciplinary Network on Alzheimer's, 2005). Verbal episodic memory impairment, especially delayed free recall, has demonstrated effectiveness for evaluating potential AD converters (Backman, Jones, Berger, Laukka, & Small, 2005; Landau et al., 2010; Perri, Serra, Carlesimo, Caltagirone, & Early Diagnosis Group of the Italian Interdisciplinary Network on Alzheimer's, 2007; Small, Mobly, Laukka, Jones, & Backman, 2003). In addition, individuals with memory and other cognitive domain impairments, especially executive dysfunction, have greater AD conversion rate (Arnaiz & Almkvist, 2003; Tabert et al., 2006). Briefly, episodic

memory is a prominent function to be assessed in individuals who are at high risk for developing AD, and performance on other cognitive functions such as executive function also provide us valuable information about disease progression over time.

1.2. Medial temporal lobe and associative memory

Episodic memory is responsible for storage of the information about what person had experienced in the past with temporal and spatial relations (Tulving, 1972). It has been known that medial temporal lobe (MTL) structures, including the hippocampal formation and adjacent cortices (i.e. entorhinal cortex, perirhinal cortex, and parahippocampal cortex), are critical for establishing memory for facts and events, and acquiring new information and binding unrelated features are core functions of hippocampus (Squire & Zola-Morgan, 1991).

To understand how different features bound together, researchers have devoted to study associative memory. Associative memory is an ability to combine different characteristics related to our experiences. A paired associate task is often used to test associative memory, and usually contains items with one attribute linked to them, such as location, color, or other features. The participants have to remember not only item (i.e., item memory) but also associative information that they have learned, and it has been demonstrated that both information could be examine separately (Humphreys, 1976). According to the dual-process model of recognition memory

that account for dissociative performance of recognition memory, item judgment is relied on both processes of familiarity and recollection, but associative judgment depends on recollection (Jacoby, 1991; Yonelinas, 1997). However, the familiarity process might also contribute to unitized association (Quamme, Yonelinas, & Norman, 2007). In the domain dichotomy view of associative recognition memory, within-domain and between-domain associations were formed based on the characteristic similarity of items which bound together, and the familiarity process supported within-domain associations (A. Mayes, Montaldi, & Migo, 2007).

With respect to functional contributions within medial temporal subregions, the perirhinal cortex has been shown to be related to object memory while the parahippocampal cortex is responsible for spatial memory (see review Squire, Stark, & Clark, 2004). During memory encoding, item and contextual (especially location) information are converged together in the hippocampus and then also reactivate by hippocampus during retrieval (see review Eichenbaum, Yonelinas, & Ranganath, 2007). In addition, unitized and within-domain associations were supported by the perirhinal cortex in the domain dichotomy view of associative recognition (A. Mayes et al., 2007). Previous studies have reported that an increased regional cerebral blood flow in the hippocampus, parahippocampal gyrus, and entorhinal cortex was found while performing paired associative recall in healthy participants (Henke, Buck,

Weber, & Wieser, 1997; Klingberg, Roland, & Kawashima, 1994). Moreover, selective impairment on the between-domain associative recognition with sparing item recognition memory has been found in a patient with hippocampus damaged (A. R. Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002; A. R. Mayes et al., 2004).

In spite of the controversy, studies of brain substrates correlation with the dual process model have supported the functional specialty in MTL and suggested that the familiarity process is related to entorhinal cortex while the recollection process relying more on posterior hippocampus and parahippocampal cortex although prefrontal cortex involvement has also been implied (Dimitrov et al., 1999; Ranganath et al., 2004; Yonelinas et al., 2007). Thus, memory performance could be dissociated into different components, and the impairment of associative memory should be sensitive to medial temporal dysfunction, especially hippocampus.

1.3. Associative memory performance of AD and MCI

Researchers have found poor visual paired associate learning (geometric figure-location association; meaningful picture association) and verbal paired associate performances in individual with early AD compared to healthy controls or other types of dementia (Duchek, Cheney, Ferraro, & Storandt, 1991; Fowler, Saling, Conway, Semple, & Louis, 1997; Fowler, Saling, Conway, Semple, & Louis, 2002; Lindeboom, Schmand, Tulner, Walstra, & Jonker, 2002; G. J. Lowndes et al., 2008; McWalter et

al., 1991). The result based on a functional MRI study in individuals with mild AD while encoding novel face-name pairs also demonstrated similar findings (Sperling et al., 2003). According to neurocognitive framework, G. Lowndes and Savage (2007) also suggested that associative recognition relative to item recognition might be sensitive to integrity of MTL where is damaged in early course of AD. These studies together have suggested that paired associative task is a sensitive tool to detect dementia of Alzheimer type.

Moreover, different processes related to impairment of associative memory have been investigated. For instance, Gallo, Sullivan, Daffner, Schacter, and Budson (2004) illustrated impairments of recall-to-reject process in patients with mild AD induced more familiar-based false alarm on an verbal paired associative task than that in healthy aging although they didn't examine monitoring-related function. Studies endorsed the dual-process model have revealed that relatively sparing familiarity to recollection process in individuals with a-MCI and AD (Anderson et al., 2008; Serra et al., 2010; Westerberg et al., 2006) although different findings had also been reported with general impairments on both processes (Ally, Gold, & Budson, 2009; Wolk, Signoff, & Dekosky, 2008). In addition, recollection-based memory paradigm has been showed to have greater discriminative power for distinguishing AD patients from healthy elders compared to the standard tests (Tse, Balota, Moynan, Duchek, &

Jacoby, 2010). In order to obtain memory defective profiles (i.e., encoding or retrieval deficit) in paired associative memory to identify high-risk a-MCI, Pike, Rowe, Moss, and Savage (2008) compared cue-recall performance to recognition in a-MCI and AD patients. Conversely, various defective profiles were found in their sample and such findings were contributed to the issue of sample heterogeneity by the authors (Pike et al., 2008). Based on Pike and colleagues findings, it raises a question about characteristics of participants and associative memory impairment relative to item memory in literatures. When enrolling participants, most studies conducted only memory or general cognition screening examinations. However, such approach makes it difficult to separate healthy older adults from individuals with mild cognitive impairment or pathological aging became since examination of other domains of cognitive functions are not included. The heterogeneity of cognitive impairments in MCI individuals might also produce different performances; for example, the study revealed the severity of cognitive impairments in MCI affected their performance on item and associative memory (Clement & Belleville, 2012). As a result, contradiction findings were found (H. M. Wang, Yang, Kuo, Huang, & Kuo, 2013). It is also unclear that whether cognitive dysfunction other than memory in patients might influence on associative memory impairment (Collie, Myers, Schnirman, Wood, & Maruff, 2002; Hanaki et al., 2011; O'Donnell, Pietrzak, Ellis,

Snyder, & Maruff, 2011).

Poor item memory in participants with AD or MCI than in normal controls during learning could result in their deficits in associative memory (Atienza et al., 2011). However, previous studies have presented impaired paired associative memory in individuals with AD and MCI without reporting item memory performance (Duchek et al., 1991; Fowler et al., 1997; Fowler et al., 2002; Lindeboom et al., 2002; G. J. Lowndes et al., 2008; McWalter et al., 1991; O'Donnell et al., 2011). Troyer and colleagues (2008) found greater associative memory impairment in a-MCI individuals relative to item memory compared to controls. The significant group difference was also found on associative memory score corrected for recalled items, but the corrected scores decreased sensitivity and specificity in identifying a-MCI (Troyer et al., 2008). It should be noted that the floor effect of item memory in a-MCI individuals might cause detrimental consequences to their corrected scores. Studies that matched item memory performance statistically have demonstrated poor associative memory performance in individuals with MCI and such findings were correlated with smaller volume and decreased activation in hippocampus (Hanseeuw et al., 2011; Troyer et al., 2012). Therefore, evaluating the associative memory performance in individuals with MCI by revising these limitations could guide us to understand their memory dysfunction

comprehensively.

1.4. Memory studies related to features of Chinese characters

With respect to verbal associative memory, studies aforementioned are based on alphabetic languages users, and research about Chinese speakers with MCI is lacking. Chinese character is logograph system and is very different from alphabetic language. The character is constructed by either different components, such as radicals, or an unitary pattern, and its morphosyllabic in nature leads to homophonic relation between characters (Hung, Tzeng, & Tzeng, 1992). Previously, studies have presented that not only phonology but orthography of Chinese characters contributed to verbal short-term memory (Chen, 2007); orthography effect was prominent even when phonological information could not help participants to retain the character (Lai, 2008). In addition, the linguistic representation, such as knowledge of strokes and radicals, rather than pure visual similarity accounted for orthographical similarity effect (Lai, 2008). It was also supported by the finding that more brain activated in right superior parietal lobule and left middle frontal gyrus compared to verbal and spatial short-term memory respectively while participants were maintaining orthographically similar Chinese characters (Lin, 2010). According to findings which supported distinct contributions of different features of Chinese character (Chen, 2007; Lai, 2008; Lin, 2010), it would be valuable to investigate what the

Chinese character features influence on the verbal associative memory.

1.5. The purpose of this study

According to the vulnerability of MTL in AD neuropathology and its role in associate learning, associative memory measurement would be sensitive to detect AD-related memory changes. The present study applied verbal paired associate paradigm to investigate associative memory performance in individuals with MCI compared to normal aging. Different foil types based on features of Chinese character were included for the associative recognition measures to investigate their effects on the task. This study also attempted to promote item memory performance during immediate recognition and subsequently compared associative memory between the MCI and the healthy control (HC) groups. Further, data of a comprehensive neuropsychological battery and structural imaging were collected to investigate cognitive deficits in the MCI individuals and neural correlates related to verbal associative memory. With these measures, we predicted the MCI group would have worse associative memory relatively to item memory compared to the HC group and such performance would predominantly correlate with the morphometric measures of medial temporal structures. Furthermore, we hypothesized that the MCI group would make higher rearranged false alarms compared to the HC group based on the dual-process theory (Yonelinas, 1997). Though relevant study that investigate

how features of Chinese character influenced on verbal associative memory is lacking, we hypothesized that the MCI group would commit more semantically-related errors since the findings of vulnerable semantic system in MCI and AD have been suggested (Adlam, Bozeat, Arnold, Watson, & Hodges, 2006; Hodges, Salmon, & Butters, 1992). We also hypothesized that both two groups might make more orthographically-related and/or phonologically-related errors compared to novel errors based on previous finding of orthographic and phonological similarity effect on short-term memory (Lai, 2008); furthermore, the MCI group might have higher false alarms in both error types compared to the HC group due to their poor associative memory.

2. Methods

2.1. Participants

The study included 22 participants with MCI and 25 age- and education-matched healthy controls (HC) with age ranged from sixty to eighty-six years old and education ranged from six to eighteen years. Participants were recruited from National Taiwan University Hospital, Taipei City Hospital – Renai Branch, and communities. Participants were excluded if there were any current evidence of disturbance of consciousness, major medical diseases, neurological diseases, psychiatry disorders, or history of substance abuse or head injury. The present study was a part of an ongoing aging study, which was approved by the institutional review board of National Taiwan University Hospital and Taipei City Hospital. All participants signed informed consent forms before attending this study.

The participant was classified as MCI based on the criteria recommended by International Working Group (Winblad et al., 2004), in which MCI was defined when 1) neither normal aging nor dementia; 2) cognitive decline reported by self or an informant and defective performances on objective neuropsychological tests, or evidenced decline performances on the tasks over time; and 3) preserved basic daily activities or the slightest impaired on instrumental activities. The cognitive decline in this study was regarded as at least two neuropsychological test scores in one

cognitive domain below one standard deviation of the norm (Chang et al., in press; Jak et al., 2009). If episodic memory was one of the cognitive domains the participant showed impairment, the participant would be classified as amnestic-MCI (a-MCI) ; otherwise, non-amnestic-MCI (na-MCI) would be considered (Petersen, 2004). Additionally, single domain or multiple domain was also determined by whether more than one cognitive domains were involved (Petersen, 2004). Our sample consisted of 11 a-MCI-single, eight a-MCI-multiple, and three na-MCI-single domain. Exception of Geriatric Depression Scale (Burke, Roccaforte, & Wengel, 1991) reported by participants, other clinical characteristics (e.g., Clinical dementia rating scale) of participant were obtained by interviewing informant of the participant. Specifically, the function of participants' activities of daily living and instrumental activities of daily living were scored by Barthel Scale (Mahoney & Barthel, 1965) and Lawton's Instrumental Activities of Daily Living Scale (Lawton & Brody, 1969) respectively; to stage the severity of cognitive impairment, the Clinical Dementia Rating Scale Sum of Boxes score was calculated (O'Bryant et al., 2008). To evaluate the cerebrovascular risk factors and calculate the stroke probability (D'Agostino, Wolf, Belanger, & Kannel, 1994), blood pressure and other clinical information were obtained through the participants. Mean arterial blood pressure (MABP) was calculated using the formula: 1/3 (systolic pressure- diastolic pressure) + diastolic

pressure. MABP is believed to indicate perfusion pressure, particularly in body organs, and therefore may be more directly related to brain structure (Stricker et al., 2013). In addition, such index has been suggested for its importance related to stroke prediction in elders (Miura et al., 2004), white matter integrity (Guo et al., 2009), and cognition (Brown et al., 2010).

2.2. Neuropsychological evaluation

All participants were tested with a comprehensive neuropsychological battery, which included general intellectual function, language, attention, executive function, visual construction, learning and memory. The general intellectual function was estimated by demographic variables (Chen, Hua, Zhu, & Chen, 2008) and four subtests of the Wechsler Adult Intelligence Scale-Third Edition, Taiwan version (WAIS-III; Chen & Chen, 2002): the Similarities, the Matrix Reasoning, the Arithmetic, and the Digit-Symbol Substitution subtests. The language ability included semantic knowledge and naming ability, and was measured by the Vocabulary subtest of the WAIS-III and the 30- item Boston Naming Test, Chinese version (30- item BNT; Y. J. Chiu, 2008). In respect to attention function, the Digit Span subtest of the WAIS-III (Chen & Chen, 2002) and the Spatial Span subtest of the Wechsler Memory Scale -Third Edition, Taiwan version (WMS-III; Hua et al., 2005) were administered. The executive function was comprised of working memory,

concept formation, set shifting, abstract reasoning, design and word generating abilities in this study. It was assessed with the Modified Card Sorting Test (MCST; Nelson, 1976; Kao, 2009), the Part 2 of the Color Trails Test (CTT-2; D' Elia, Satz, Uchiyama, & White, 1996; Kuo, 2009), the Matrix Reasoning and the Similarities subtests of the WAIS-III, the Design Fluency Test of the Delis-Kaplan Executive Functions System (D-KEFS; Delis, Kaplan, & Kramer, 2001), and the animal fluency. In addition, the working memory performance was scored by the Working Memory Index of the WAIS-III, which was derived from the Arithmetic and the Digit Span subtests of the WAIS-III. With regard to the visuomotor ability, the Part 1 of the Color Trails Test (CTT-1; D' Elia et al., 1996; Kuo, 2009), and the Digit-Symbol Substitution subtest of the WAIS-III, were administered. The visual spatial construction function was examined by the Block Design subtest of the WAIS-III (Chen & Chen, 2002). Finally, to assess the verbal and non-verbal memory ability, we included the Logical Memory, the Visual Reproduction, and the Verbal Paired Associate subtests of the WMS-III (Hua et al., 2005), and the Visual Paired Associate subtest of the Wechsler Memory Scale-Revised (WMS-R; Steinberg, Bieliauskas, Smith, & Ivnik, 2005; Wechsler, 1987).

2.3. Word association task

The task was presented visually on a notebook screen by E-Prime 2.0

(Psychology Software Tools, Pittsburgh, PA). The stimuli included 144 Chinese characters selected from the database of the Concised Mandarin Chinese Dictionary edited by National Language Committee, Ministry of Education, Taiwan (National Language Committee, 1997). There was three phases within the task, including the studying phase, the immediate item and associative recognition phase, and the delayed item and associative recognition phase. During the studying phase, participants were asked to learn eight character pairs (e.g., 太-聞, 知-要) for three times, and each pairs were presented for 4 seconds with a 1 second inter-stimulus interval. Immediately following the studying phase, participants were tested for their item memory, which consisted of 16 studied and 16 unstudied characters and was self-paced. The unstudied characters were matched with studied characters on strokes and radicals. If the accuracy rate of the item recognition test was above 80%, the participant would proceed to the immediate associative recognition task; otherwise the participant would receive an additional learning trial to facilitate their performance and followed by another item recognition test with fillers different from the previous trials. The Figure 1 presents the schematic illustration of the task paradigm. Four learning trials maximum were used for all participants given that loss of benefit from more learning trials was found in the pilot study. In the associative recognition phase, participants were asked to discriminate the original

pairs from other foils. Participants were instructed to press the “old” key only when the pair was presented as the same pair during the studying phase (i.e., an original pair), or to press the “new” key if the pair was not presented together previously or a novel pair. The associative recognition phase was also self-paced. There were five types of foil, and each type contained eight trails: 1) novel pairs: new pairs were established by characters which never presented in other phase; 2) rearranged pairs: characters from original pairs were recombined with one another (e.g., 知-聞); 3) orthographically-related pairs: pairs were consisted of one studied character and a character orthographically similar to another original character (e.g., 大-聞); 4) phonologically-related pairs: pairs were designed as orthographically-related pairs, but homophone character was substituted for one of the original characters (e.g., 泰-聞); 5) semantically-related pairs: the design was also similar to fourth and fifth type, but character of pair had semantic relation similarly to the original character (e.g., 極-聞). The semantically-related characters were selected from a Chinese dictionary (T. H. Chiu, 2008), and the orthographically- and phonologically-related characters were chosen based on consensus of the research team. Two versions of foil pair were developed in considering counterbalance of which character in the original pairs were replaced by the foil, and they were applied at the immediate and the delayed associative recognition phases respectively. The associative memory was an

intentional task that participants were instructed to remember as many original pairs as possible during study phase and in the end of the immediate associative recognition test, of which they were reminded to be tested again later. After 30 to 35 minutes, the participants were given item and associative recognition tests again, and the procedure was the same as in the immediate recognition phase. All stimuli were presented in a same pseudorandom order.

2.4. Modified Verbal Paired Associate subtest of the WMS-III

Except development of a word association task, we modified the Verbal Paired Associate (PA) subtest of the WMS-III by introducing other foils in the recognition phase. The original recognition phase consisted of 12 original pairs (e.g., 銀行-卡通; 蜈蚣-領隊) and 12 novel pairs (e.g., 天氣-馬戲), and ceiling effect was reported (Uttl, Graf, & Richter, 2002). Thus, we added 16 semantically-related foils and six rearranged foils (e.g., 蜈蚣-卡通) into the test, and a pseudorandom sequence was applied. The semantically-related foils consisted of one original word and the other word that was semantic category related with the word from original pair (e.g., 銀行-漫畫). Because there were four word pairs presented repetitively on the original recognition phase, the frequency of each stimulus presented was not the same. The two-character Chinese words were also chosen based on consensus of the research team.

2.5. MRI data acquisition and processing

All participants were scanned on a 3-Tesla Magnetic Resonance Imaging system (Magnetom Trio, Siemens, Erlangen, Germany) with a 32-channel head array coil which was used as a signal receiver. Head movements were minimized with expandable foam cushions. The section orientation of T1-weighted structure images was parallel to the anterior/posterior commissure line. The high resolution T1-weighted structure images were obtained with a Magnetization-Prepared rapid gradient echo (MP-RAGE) sequence (coronal slicing, TR/TE = 2000/2.98 ms, flip angle = 9°, field of view = 192×256 mm^2, matrix size = 192×256, voxel size = 1×1×1 mm^3).

The data was processed by using the FreeSurfer image analysis suite (version 5.1.0, http://surfer.nmr.mgh.harvard.edu/), which is freely available for download online. The processing included cortical reconstruction, subcortical segmentation (Fischl et al., 2002; Fischl, Salat, et al., 2004), and parcellation of the cerebral cortex into region of interests (ROIs; Desikan et al., 2006; Fischl, van der Kouwe, et al., 2004). We focused on the brain regions where have been related with AD pathological changes, such as entorhinal cortex, parahippocampal cortex, and hippocampus in the medial temporal lobe (Braak & Braak, 1991; Hyman, Van Hoesen, Damasio, & Barnes, 1984); in addition, regions of cingulate cortex and frontal lobes

were also analyzed due to their relationship with early AD pathology (McEvoy et al., 2009; Whitwell et al., 2008). To reduce the number of comparisons, the pars opercularis and pars triangularis of frontal regions were combined as operculum; the caudal and rostral anterior cingulate regions were combined as anterior cingulate cortex; the isthmus and posterior cingulate regions were combined as posterior cingulate cortex.

2.6. Procedure

All participant was first administered a comprehensive neuropsychological test battery to examine their cognitive function. The word association task was given on a different day to minimize fatigue. After receiving the cognitive tests, participants were also asked to receive magnetic resonance imaging (MRI) scans. All data was collected within three months after receiving cognitive evaluation.

2.7. Statistical Analyses

To examine group differences in demographic and clinical characteristics data, independent t test or Chi-square test was conducted. Independent t tests were also performed when compared two groups among all indexes of neuropsychological test, and adjusted t-test was reported if the Levene's test for equality of variance reached significant level. To avoid inflated type I error, the alpha was set at .0016 (Bonferroni adjustments for Type I error). Although the distribution of some

variables wasn't normally distributed, the results with parametric and nonparametric analyses did not differ. Accordingly, we only reported results based on parametric analyses here. All neuropsychological data were presented with raw scores though the classification of participants was based on age- and education-corrected norm.

With regard to the performances on the word association task, the alpha was set at .05. The accuracy rates were calculated from percentage of correct responses for item recognition test. The performance on associative recognition was further calculated from hit rate, total false alarm rate, discriminability (*d'*), and response bias (β). The hit rate was calculated from the percentage of correctly identified target pairs for each participant; the total false alarm rate was calculated from the percentage of incorrectly identified foils as targets in all foils for each participant. To calculate *d'*, hit rate and false alarm rate were converted to z-scores and following by formula: *d'* = Z(hit rate) - Z(false alarm rate) (Stanislaw & Todorov, 1999). If extreme value was found which the hit rate was equal to 100% or the false alarm rate was equal to 0%, an adjustment score was computed according to the suggestion of previous study (Macmillan & Kaplan, 1985). The response bias was calculated following the equation: $\beta = e^{\left\{\frac{[\varphi^{-1}(\text{false alarm})]^2 - [\varphi^{-1}(\text{hit})]^2}{2}\right\}}$ (Stanislaw & Todorov, 1999). In addition, we calculated the false alarm rate of each foil type that derived from percentage of the number of false recognition in a given foil type for all foils. Independent t tests were

performed to compare the item memory performance by groups. Separate two-way analyses of variance (ANOVAs) were performed with group (MCI, HC) as a between-subjects factor and time (immediate, delayed) as a within-subject factors for the accuracy, hit rate, and *d*' of the associative recognition. To determine the effects of groups, foil types, and time on the associative recognition, a three-way ANOVA was performed with group (MCI, HC) as a between-subjects factor, and time (immediate, delayed) and foil type (semantically-related, phonologically-related, orthographically-related, rearranged, novel) as within-subject factors for false alarm rate of associative recognition. The Greenhouse-Geisser correction was applied for violation of Sphericity in Repeated Measure ANOVAs.

To compare the performance on the modified Verbal PA subtest of the WMS-III, the accuracy, hit rate, and total false alarm rate were calculated by the same method as above mentioned. The false alarm rates of each foil type were calculated from the percentage of falsely recognitions in a given foil type due to the number of different types of foils was different. The independent t tests were performed to examine the performance by groups.

With regard to the brain morphometric data, the cortical thickness and subcortical volumetric data were regressed out the gender effect, and the estimated total intracranial volume (eTIV; Buckner et al., 2004) was also regressed out from the

volumetric data to correct for individual difference in head size. Thus, standardize residuals (z-scores) were used for further analyses. To identify brain morphometric differences between groups, independent t tests were performed. Pearson correlations were also conducted to examine the relationship between performances on the word association task and brain morphometric measures. All statistical analyses were conducted in SPSS (version 20.0; IBM Corp.).

3. Results

3.1. Demographic and clinical characteristics data

The two groups were matched on age, education, gender distribution, scores on the Geriatric Depression Scale, the Framingham Heart Study 10 years stroke risk probability, the Barthel Scale, and the Lawton's Instrumental Activities of Daily Living Scale (all *p*-values > .05). However, the MCI group had higher MABP ($t_{(45)}$ = 2.42, p = .02) than the HC group (Table 1). As expected, the MCI group obtained significantly higher CDR-Sum of Boxes scores compared to the HC group ($t_{(27.39)}$ = 2.45, p = .021).

3.2. Performances on the neuropsychological test battery between groups

The MCI group showed significantly poorer scores on the Working Memory Index of the WAIS-III ($t_{(42)}$ = -4.01, p < .001), the number of finished category of the MCST ($t_{(31.63)}$ = -3.85, p = .001), and the switching condition of the Design Fluency ($t_{(42)}$ = -3.75, p = .001) compared to the HC group (Table 2). With regard to memory function, the MCI group showed poorer performances on all memory measures (p < .0016; details see Table 2) compared to the HC group except for the delayed recognition of the Visual Reproduction and the Verbal Paired Associates (Verbal PA) subtests of the WMS-III. There was no significant difference on performance of other neuropsychological tests between groups.

3.3. Brain morphometric differences between groups

All but three participants (1 MCI and 2 HC) didn't undergo MRI scan due to participants' subjective concerns for their health and time unavailability. The morphometric measures included volumetric measures of bilateral hippocampal formation, including dentate gyres, CA fields, subiculum/ parasubiculum and the fimbria (Makris et al., 1999), and thickness measures of frontal, temporal areas, and bilateral cortex regions (see Regions of interests (ROIs) listed in Table 3). In addition, to observe more specifically difference in the entorhinal cortex, the cytoarchitectural-defined measures were included for analysis (Fischl et al., 2009). There were significant differences between groups across regions of frontal lobe and medial temporal lobes. Specifically, the MCI group had thinner cortical thickness in left lateral orbital frontal cortex ($t_{(33.57)}$ = -2.29, p = .029, Cohen's d = 0.69) than the HC group. The group difference in left frontal pole was marginal significant (p = .05). The MCI group also showed smaller volume of right hippocampus ($t_{(42)}$ = -2.35, p = .024, Cohen's d = 0.71) and thinner cortical thickness of left entorhinal cortex ($t_{(42)}$ = -2.18, p = .035, Cohen's d = 0.66) than the HC group (Figure 2).

3.4. Performance on the word association task

3.4.1. Item memory. Table 4 presents the results of the performance on the word association task. The two groups had significant difference in the number of

total learning trials used ($t_{(40.20)}$ = 2.54, p =.015, Cohen's d = 0.74). The result of two-way ANOVA for the accuracy rate of item recognition revealed a significant group effect ($F_{(1, 45)}$ = 9.53, p = .003, η^2 = .18) with a lower accuracy rate in the MCI group and a significant time effect ($F_{(1, 45)}$ = 18.95, p < .001, η^2 = .30) with a lower accuracy rate in the delayed recognition for all participants. The group by time interaction was also significant ($F_{(1, 45)}$ = 12.91, p = .001, η^2 = .22). Following univariate ANOVA revealed that the MCI group ($F_{(1, 45)}$ = 31.38, p < .001) showed greater memory decay after a 30-minute delay for the items. Specifically, compared to the HC group, the MCI group showed a comparable accuracy rate in the immediate condition but lower in the delayed condition ($F_{(1, 90)}$ = 16.51, p < .001; Figure 3) for item memory.

3.4.2. Associative memory.

3.4.2.1. Discriminability (d') of associative recognition. To investigate the group difference in discriminating foils and target pairs, a two-way ANOVA for *d'* was performed. A main effect for group ($F_{(1, 45)}$ = 19.90, p < .001, η^2 = .31) was found with the MCI group showing significantly lower *d'* than the HC group. A main effect for time ($F_{(1, 45)}$ = 30.63, p < .001, η^2 = .41) was also found and the results revealed that the *d'* for the associative memory in the delayed condition was significantly lower than that in the immediate condition (Figure 4). However, there

was no significant group by time interaction ($p > .05$).

3.4.2.2. Response bias (β) of associative recognition. The result of two-way ANOVA for β revealed only a significant group effect ($F_{(1, 45)} = 4.35$, $p = .043$, $\eta^2 = .09$) with lower β in the MCI group. There was no significant time effect and group by time interaction ($ps > .05$).

3.4.2.3. Hit rate of associative recognition. A two-way ANOVA for hit rate of associative recognition only revealed a significant main effect for time ($F_{(1, 45)} = 6.98$, $p = .011$, $\eta^2 = .13$), indicating lower hit rate in the delayed associative recognition than in the immediate associative recognition without group difference.

3.4.2.4. False alarm rate of associative recognition. The result of a two-way ANOVA for total false alarm rate of associative recognition showed significant group effect ($F_{(1, 45)} = 17.35$, $p < .001$, $\eta^2 = .28$) with larger total false alarm rate in the MCI group; significant time effect ($F_{(1, 45)} = 17.62$, $p < .001$, $\eta^2 = .28$) with larger the total false alarm rate in the delayed recognition across groups. A significant group by time interaction ($F_{(1, 45)} = 5.26$, $p = .027$, $\eta^2 = .11$) was found. Post hoc analyses revealed that compared to the HC group, the MCI group ($F_{(1, 45)} = 19.81$, $p < .001$) committed more false alarm errors in the delayed condition than in the immediate recall condition. The MCI group committed more false alarms compared to the HC group with greater difference in the delayed recognition ($F_{(1, 90)} = 22.08$, $p < .001$, η^2

= .24) than in the immediate recognition ($F_{(1, 90)}$ = 9.80, p = .002, η^2 = .11; Figure 5).

3.4.2.4.1. Main effects of group, time, and foil type in the false alarm rate. The result of three-way ANOVA revealed significant group effect ($F_{(1, 45)}$ = 17.35, p < .001, η^2 = .28) with larger overall false alarm rate in the MCI group as well as a significant time effect ($F_{(1, 45)}$ = 17.62, p < .001, η^2 = .28) with larger false alarm rate in the delayed recognition across groups. A main effect for foil type was also significant ($F_{(2.18, 98.12)}$ = 83.96, p < .001, η^2 = .65) that the largest false alarm was found in the rearranged type, following by the orthographically-related type; the smallest false alarm rate was showed in the novel type.

3.4.2.4.2. Two-way interaction. The group by foil type interaction was significant ($F_{(2.18, 98.12)}$ = 6.95, p = .001, η^2 = .13) with the MCI group committing more semantically-related, orthographically-related, and rearranged errors than the HC group. A significant group by time interaction ($F_{(1, 45)}$ = 5.26, p = .027, η^2 = .11) was also found. The MCI group committed more false alarms compared to the HC group with greater difference in the delayed recognition ($F_{(1, 45)}$ = 18.88, p < .001, η^2 = .38) than in the immediate recognition ($F_{(1, 45)}$ = 8.38, p = .006, η^2 = .17). Moreover, a significant time by foil type interaction was also noted ($F_{(3.31, 148.72)}$ = 21.12, p < .001, η^2 = .32) with higher false alarm rates of the semantically-related type and of the orthographically-related type in the delayed recognition compared to the

immediate recognition across groups.

3.4.2.4.3. Three-way interaction. The group by time by foil type interaction was significant ($F_{(3.31, 148.72)} = 2.61$, $p = .048$, $\eta^2 = .06$). For the delayed association, the MCI group had significantly higher false alarm rate than the HC group on the semantically-related (MCI: $M = 5.57$, $SD = 5.45$; HC: $M = 0.80$, $SD = 1.57$; $p < .001$), the orthographically-related (MCI: $M = 8.75$, $SD = 4.86$; HC: $M = 4.60$, $SD = 2.36$; $p = .002$), and the rearranged types (MCI: $M = 10.80$, $SD = 6.04$; HC: $M = 5.00$, $SD = 5.73$; $p = .002$; Figure 6). Compared to the immediate condition, the MCI group made more semantically-related type (delayed: $M = 5.57$, $SD = 5.45$; immediate: $M = 2.16$, $SD = 3.21$; $p < .001$; Figure 6a) and orthographically-related type (delayed: $M = 8.75$, $SD = 4.86$; immediate: $M = 3.86$, $SD = 3.51$; $p < .001$; Figure 6b) false alarms in the delayed condition; however, the HC group only showed elevated false alarm for the orthographically-related foils in the delayed recognition (delayed: $M = 4.60$, $SD = 2.36$; immediate: $M = 1.50$, $SD = 1.91$; $p < .001$; Figure 6b).

3.5. Associative memory after controlling for delayed item memory

As presenting in Table 4, there was a significant difference on the delayed item recognition accuracy between groups. Therefore, two-way analyses of covariance (ANCOVAs) were performed for associative memory indexes by using the accuracy of delayed item recognition as a covariate to further examine the effect of difference

of delayed item accuracy on associative memory. The results were largely similar to previous findings except for lacking of the main effects of time on the discriminability and hit rate.

However, covariance analysis adjusting for accuracy of immediate item recognition changed the significance results of three-way ANOVA. The significant effects for group ($F_{(1, 44)}$ = 9.81, p = .003, η_p^2 = .18) and group by foil type interaction ($F_{(2.08, 143.10)}$ = 5.07, p = .007, η_p^2 = .10) were remained, but other effects were not significant anymore. Despite the effect in three-way interaction was not significant (p = .095), the follow-up analyses were conducted to explore the differences after controlling the delayed item memory. The results was largely similar to previous findings without covariate that the MCI group made more semantically-related (MCI: M = 4.95, SD = 0.87; HC: M = 1.35, SD = 0.81), orthographically-related (MCI: M = 8.57, SD = 0.87; HC: M = 4.76, SD = 0.81), and rearranged (MCI: M = 10.64, SD = 1.36; HC: M = 5.14, SD = 1.27) false alarms in the delayed condition compared to the HC group.

3.6. Relationship between the word association task and brain regions

3.6.1. For all participants across the MCI and the HC groups. Table 5 presented the Pearson correlation coefficients between the measures of the word association task and brain morphometric variables for all participants across the MCI

and the HC groups. For item memory, the accuracies of both the immediate and the delayed recognition were significantly correlated with the cortical thickness of left caudal middle frontal (r = .42, p < .01), right rostral middle frontal (r = .39, p < .01), and bilateral entorhinal cortex (left: r = .47, p < .01; right: r = .41, p < .01); the delayed one was also significantly correlated with cortical thickness of right frontal operculum (r = .33. p < .05) and bilateral parahippocampal regions (left: r = .32, p < .05; right: r = .30; p < .05) as well as left hippocampal volume (r = .32, p < .05).

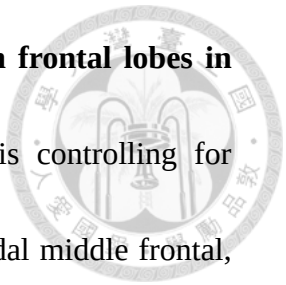
For the associative memory, the hit rate of the immediate associative recognition was significantly correlated with bilateral entorhinal cortex (left: r = .32, p < .05; right: r = .54, p < .01); the hit rate of the delayed associative recognition was correlated with right entorhinal cortex (r = .42, p < .01). The total false alarm rates of the immediate and the delayed associative recognition both had significantly negative relations to left hippocampus volume (immediate: r = -.47, p < .01; delayed: r = -.41, p < .01) and frontal regions included right frontal pole (immediate: r = -.33, p < .05; delayed: r = -.35, p < .05), caudal middle frontal (immediate: r = -.36, p < .05; delayed: r = -.36; p < .05), and superior frontal cortex (immediate: r = -.32, p < .05; delayed: r = -.33, p < .05). Additionally, the total false alarm of the delayed associative recognition was correlated with ROIs in frontal lobe, such as right rostral middle frontal (r = -.36, p < .05) and frontal operculum (r = -.36, p < .05).

The discriminabilities of the immediate and the delayed associative recognition were also significantly correlated with cortical thickness of bilateral entorhinal cortices (immediate: left: r = .50, right: r = .50, ps < .01; delayed: left: r = .37, right: r = .32, ps < .05) and bilateral hippocampus volumes (immediate: left: r = .38, right: r = .35, ps < .05; delayed: left: r = .37, right: r = .33, ps < .05). The discriminability of the delayed associative recognition was additionally correlated with right frontal pole (r = .34, p < .05), left caudal middle frontal (r = .33, p < .05), bilateral rostral middle frontal (left: r = .37, p < .05; right: r = .39, p < .01), right lateral orbital frontal (r = .31, p < .05), left superior frontal (r = .34, p < .05), and right frontal operculum (r = .47, p < .01). In addition, the immediate response bias was significant correlated with only left lateral orbital frontal cortex (r = .31, p < .05).

3.6.2. Partial correlation controlling the contribution from frontal lobes for all participants in both groups. To evaluate the unique contributions of medial temporal structures to associative memory, partial correlations controlling cortical thickness of frontal regions that demonstrated significant findings in previous text, included bilateral frontal pole, bilateral caudal and rostral middle frontal, bilateral superior frontal, bilateral lateral orbital frontal, and right frontal operculum, were conducted. As Table 6 shows, the measures of associative memory were still significantly correlated with morphometric measures of medial temporal lobes (i.e.,

bilateral entorhinal cortex and hippocampus) although the significance of correlations between the discriminability of the delayed associative recognition and bilateral entorhinal and hippocampal regions were attenuated to marginal effect (p = .05 to .09). In addition, the relation between the response bias in the immediate associative recognition and right entorhinal cortex reached a significant level (r = -.32, p < .05).

3.6.3. Relationship between the word association task and brain regions for individuals with MCI. Considering differences of clinical characteristics between MCI and HC groups, Pearson correlation analyses were also performed separately for each group. Table 7 shows the correlational results with only the MCI group. The results of medial temporal lobe were largely similar to previous findings based on all participants (Table 5); except for that results related to bilateral parahippocampal cortex and right hippocampus were no longer significant. Additionally, the accuracies of the immediate and the delayed item recognition were significantly correlated with left caudal middle frontal cortex (immediate: r = .55, p < .01; delayed: r = .61, p < .01); the delayed item recognition accuracy was correlated with right rostral middle frontal cortex (r = .45, p < .05). The response bias of the immediate associative recognition was significantly correlated with right entorhinal cortex (r = -.45, p < .05), and the delayed one was correlated with bilateral entorhinal cortex (left: r = -.46, p < .05; right: r = -.49, p < .05).



3.6.4. Partial correlation controlling the contribution from frontal lobes in individuals with MCI. A separate partial correlational analysis controlling for frontal regions (left frontal pole, left lateral orbital frontal, left caudal middle frontal, and right rostral middle frontal regions) was also performed for all the participants with MCI. The associative memory measures remained significant correlated with the medial temporal lobes and similar results were obtained (Table 8), except for the relations between the accuracy of item recognition in the delayed condition and left entorhinal and hippocampal regions now became marginally significant (p = .05 to .06).

3.6.5. Relationship between the word association task and brain regions for the healthy controls. With respect to the HC participants, no significant correlation between the item memory and any morphometric variables was observed (Table 9). With respect to the associative memory, the hit rate of the delayed associative recognition was correlated with right frontal operculum (r = .43, p < .05). The total false alarm rates of the immediate and the delayed associative recognition were both negatively correlated with left pars orbitalis (immediate: r = -.44, p < .05; delayed: r = -.41, p < .05); the delayed one was additionally correlated with left anterior cingulate cortex (r = -.44, p < .05). In addition, the discriminability of the immediate associative recognition was significantly correlated with right entorhinal

cortex (r = .43, p < .05); the delayed one was correlated with bilateral rostral middle frontal (left: r = .43, p < .05; right: r = .50, p < .05) and right lateral orbital frontal cortex (r = .45, p < .05). They both correlated with right pars orbitalis (immediate: r = .42, p < .05; delayed: r = .52; p < .05) and frontal operculum (immediate: r = .47, p < .05; delayed: r = .62, p < .01). The response bias in the immediate associative recognition was significantly correlated with left lateral orbital frontal (r = .46, p < .05) and left medial orbital frontal (r = .49, p < .05) regions.

3.6.6. Partial correlation controlling the contribution from frontal lobes in health controls. Table 10 shows the results of partial correlation analysis controlling for frontal regions included left frontal pole, bilateral rostral middle frontal, bilateral lateral orbital frontal, left medial orbital frontal, right pars orbitalis, and bilateral frontal operculum performed for the HC group. The results were generally similar to the previous findings (Table 9), but the right entorhinal cortex was no longer correlated with the discriminability of the immediate association. Additionally, the total false alarm rate of the delayed associative recognition was also not significantly correlated with left anterior cingulate cortex.

3.7. Relationship between the false alarm types of the word association task and brain regions

3.7.1. For all participants across the MCI and the HC groups. The relationships between different false alarm types and brain morphometry were further examined because significant behavioral differences and relations with brain morphometry were found on the total false alarm rate as previous showed. The results for all participants are shown in Table 11. For the semantically-related false alarm, the errors made in the immediate condition were correlated with left entorhinal cortex (r = -.39, p < .01), left hippocampus volume (r = -.35, p < .05), right frontal pole (r = -.42, p < .01), right caudal middle frontal (r = -.34, p < .05), bilateral rostral middle frontal (left: r = -.35, p < .05; right: r = -.39, p < .01), right superior frontal (r = -.39, p < .01), and bilateral frontal operculum (left: r = -.41, p < .01; right: r = -.45, p < .01); the delayed false alarm was correlated with left hippocampus (r = -.42, p < .01), right middle frontal (caudal: r = -.38, p < .05; rostral: r = -.36, p < .05), bilateral superior frontal (left: r = -.32, p < .05; right: r = -.39, p < .01), and bilateral frontal operculum (left: r = -.31, p < .05; right: r = -.36; p < .05).

For the phonologically-related type, the immediate false alarm was only correlated with bilateral hippocampus volumes (left: r = -.51, p < .01; right: r = -.30, p < .05); the delayed one was also correlated with left hippocampus (r = -.41, p < .01)

and right frontal pole (r = -.33, p < .05). For the orthographically-related type, the immediate false alarm was only correlated with the frontal regions which included right frontal pole (r = -.43, p < .01), right caudal middle frontal (r = -.39, p < .01), and bilateral superior frontal cortex (left: r = -.32, p < .05; right: r = -.39, p < .01); the delayed false alarm was significant correlated with right hippocampus (r = -.31, p < .05), right frontal pole (r = -.45, p < .01), right frontal operculum (r = -.39, p < .01), and bilateral posterior cingulate cortices (left: r = -.34, p < .05; right: r = -.36, p < .05).

For the rearranged type, the immediate false alarm was correlated with left hippocampus (r = -.43, p < .01); the delayed one was correlated with right caudal middle frontal (r = -.35, p < .05) and right frontal operculum (r = -.32, p < .05). For the novel type, the immediate and the delayed false alarms were both correlated with left hippocampus (immediate: r = -.41, p < .01; delayed: r = -.41, p < .01).

3.7.2. Partial correlation controlling the contribution from frontal lobes for all participants across groups. To investigate the relations between medial temporal structures and false alarm errors, partial correlation analyses controlling cortical thickness of frontal regions included bilateral frontal pole, right caudal middle frontal, bilateral rostral middle frontal, left lateral orbital frontal, bilateral superior frontal, and bilateral frontal operculum were further performed for all participants

(Table 12). The significant correlations with left hippocampus remained, but the relations between right hippocampus and phonologically-related errors in the immediate condition as well as orthographically-related errors in the delayed condition became marginal (p = .07). The significance of relation between semantically-related false alarm in the immediate condition and left entorhinal cortex was also attenuated to marginal (p = .07). The cingulate regions also did not contribute to the performances anymore. Nonetheless, the relation between novel false alarm in the delayed condition and right hippocampal volume reached a significant level (r = -.31, p < .05).

3.7.3. Relationship between the false alarm types of the word association task and brain regions for individuals with MCI. Another set of Pearson correlation analyses were also performed separately by groups as the same as aforementioned. The correlational result for individuals with MCI was presented in Table 13.

For the semantically-related false alarm, in the immediate condition was only correlated with the frontal regions which included bilateral rostral middle frontal (left: r = -.48, p < .05; right: r = -.47, p < .05), right superior frontal (r = -.51, p < .05), and bilateral frontal operculum (left: r = -.53, p < .05; right: r = -.50, p < .05); the delayed one was correlated with left hippocampus (r = -.53, p < .05) and right superior frontal

cortex (r = -.49, p < .05).

For the phonologically-related type, the left hippocampal volume was significantly associated with the immediate (r = -.51, p < .05) and the delayed (r = -.54, p < .05) false alarms. For the orthographically-related type, only the immediate false alarm was significantly correlated with right superior frontal cortex (r = -.46, p < .05).

For the rearranged type, the immediate false alarm was negatively correlated with left hippocampus (r = -.52, p < .05) but positively correlated with right medial orbital frontal cortex (r = .46, p < .05); the delayed one was only correlated with left caudal middle frontal cortex (r = -.53, p < .05). For the novel type, both the immediate (r = -.47, p < .05) and the delayed (r = -.47, p < .05) false alarm was negatively correlated with left hippocampus; however, the delayed one was positively correlated with right frontal operculum (r = .52, p < .05).

3.7.4. Partial correlation controlling the contribution from frontal lobes in individuals with MCI. Table 14 presented the results of partial correlation controlling frontal regions included left frontal pole, left lateral orbital frontal, right caudal middle frontal, bilateral rostral middle frontal, right medial orbital frontal, right superior frontal, and bilateral frontal operculum for the MCI group. The correlational results in the left hippocampal volume were the same as the previous

findings (Table 13).

3.7.5. Relationship between the false alarm types of the word association task and brain regions for the healthy controls. Table 15 presents the correlational results of the HC group, and the relationship between the novel type false alarm and morphometry was unable to analyze because the mean value of false alarm rates was all equal to zero.

For the semantically-related type, the immediate false alarm was correlate with left entorhinal cortex (r = -.55, p < .01), bilateral anterior cingulate cortex (left: r = -.45, p < .05; right: r = -.45, p < .05), and several frontal regions including right frontal pole (r = -.56, p < .01), left lateral orbital frontal (r = -.42, p < .05), and medial orbital frontal cortex (r = -.53, p < .01); the delayed one was correlated with right rostral middle frontal (r = -.46, p < .05), bilateral frontal operculum (left: r = -.50, p < .05; right: r = -.45, p < .05), and left anterior cingulate cortex (r = -.54, p < .01).

For the phonologically-related type, only frontal-related correlations were significant in which the immediate false alarm was correlated with left middle frontal (caudal: r = -.46, p < .05; rostral: r = -.48, p < .05) and bilateral frontal pars orbitalis (left: r = -.44, p < .05; right: r = -.41, p < .05); the delayed false alarm was only correlated with left frontal operculum (r = -.42, p < .05). With respect to the orthographically-related type, the immediate false alarm was negatively correlated

with left medial orbital frontal cortex (r = -.43, p < .05) but positively correlated with right hippocampus (r = .42, p < .05); the delayed one was correlated with anterior, orbital, and superior frontal regions and cingulate regions (details see Table 15). For the rearranged type, only significant correlation between the delayed false alarm and left frontal pars orbitalis (r = -.42, p < .05) was found.

3.7.6. Partial correlation controlling the contribution from frontal lobes in healthy controls. Separate partial correlations were also performed for the HC group. After controlling for cortical thickness of all frontal ROIs except for right caudal middle frontal and left superior frontal regions (Table 16), the significant relations in the medial temporal structures remained. The left hippocampal volume was additionally correlated with semantically-related false alarm in the delayed condition (r = .43, p < .05). In contrast, the relations in cingulate regions were no longer significant except for marginal effect on semantically-related false alarm in the delayed condition (r = -.40, p = .06)

3.8. Further analysis

To examine the relationship between executive function and our associative memory task, executive function composite score was obtained from the Working Memory Index which consist of the Arithmetic and the Digit Span subtests of the WAIS-III, the Matrix Reasoning and the Similarities subtests of the WAIS-III, the

backward span of the Digit Span of the WAIS-III, the backward span of the Spatial Span of the WMS-III, the category number of the MCST, the time difference between CTT Part2 and Part1, the switching correct score of the D-KEFS Design Fluency Test, and the Semantic Fluency for animal. The participant's performance on each of the executive measures was converted to a z-score based on norms obtained from the HC participant pool in the present study. For ease of interpretation, the z-score of the CTT time differences between Part2 and Part1 was inverted prior to averaging the z-scores of these tests. The resulting composite z-scores thus represented the participant's relative performance on executive function, with positive numbers representing better performance. Pearson correlation between executive function and the word association task was conducted only for the MCI group. The results revealed that executive function was significantly correlated with associative memory performance, especially in overall discriminability (Table 17).

3.9. Brief summary of findings with the word association task

Taken together, the MCI group had worse associative memory performance compared to the HC group even after controlling delayed item memory. The performance discrepancy between groups was derived from higher false alarm rate in the MCI group, specifically in semantically-related, orthographically-related, and rearranged types in the delayed associative recognition. The MCI group also made

more semantically-related and orthographically-related errors as time passed by. Furthermore, the associative memory was associated with left hippocampal volume in the MCI group even after controlling for the effect of frontal regions. Negative correlations between left hippocampal volume and false alarm types were also found which include phonologically-related, rearranged, novel type errors in the immediate condition as well as semantically-related, phonologically-related, and novel type errors in the delayed condition.

3.10. Performance on the modified recognition of the Verbal Paired Associate subtest of the WMS-III

Table 18 presents the results of performance on the modified recognition of the Verbal PA of the WMS-III between groups. There were significant differences between two groups on the original recognition accuracy ($t_{(22.72)}$ = -2.77, p = .011, Cohen's d = 0.83) and on the modified recognition accuracy ($t_{(24.18)}$ = -3.67, p = .001, Cohen's d = 1.10; Figure 7). The two-way ANOVA was performed to examine difference in two versions of the recognition task. A significant group effect ($F_{(1, 43)}$ = 15.10, $p < .001$, η^2 = .26) with lower accuracy rate in the MCI group and a significant version effect ($F_{(1, 43)}$ = 17.51, $p < .001$, η^2 = .29) with lower performance in the modified recognition for all participants in general were found. However, no group by version interaction was found ($p > .05$)

When examining the results with the modified version, we found significant differences for the hit rate ($t_{(22.73)}$ = -2.83, p = .010, Cohen's d = 0.85) and total false alarm rate ($t_{(23.96)}$ = 2.59, p = .016, Cohen's d = 0.77). With respect for the false alarm type, the semantically-related false alarm ($t_{(25.86)}$ = 2.20, p = .037, Cohen's d = 0.66) and the rearranged false alarm ($t_{(33.07)}$ = 3.38, p = .002, Cohen's d = 1.01) were significantly different from groups, while the novel type false alarm did not show significant group difference.

4. Discussion

The present study investigated how Chinese speakers with MCI performed on verbal associative memory task with stimuli varied from different features of Chinese characters. As hypothesized, we found the MCI group presented poor verbal associative memory than the HC group even though controlling for item memory. Further, associative memory performances in individuals with MCI were correlated with left hippocampus atrophy where corresponds to AD neuropathological changes. An overall higher false alarm rate in the associative recognition was found in the MCI group relative to the control group. Importantly, the MCI group made more rearranged, orthographically-related, and semantically-related errors compared to the HC group, but only rearranged false alarm in the immediate condition and semantically-related false alarm in the delayed condition were significantly correlated with left hippocampus among these errors. Moreover, with respect to the recognition performance on the Verbal PA subtest of the WMS-III, the modified version presented significant group difference with substantial effect size compared to the original version.

4.1. Associative memory performance on the word association task

As hypothesized, the present results showed that associative memory impairment in the MCI group was not an exclusive consequence of group difference in item

memory, and the critical role in hippocampus in associative memory was indicated. After controlling group difference in delayed item memory, the MCI group still presented worse associative memory performance compared to the HC group, which was in accord with previous studies (Hanseeuw et al., 2011; Troyer et al., 2012) and the view of impairment of recollection but spared in familiarity process in MCI (Anderson et al., 2008; Serra et al., 2010). It is noted that the delayed item memory affected the differences between false alarm types. Since the foil of Chinese character was just substituted for one character of the original character pair, the similarity of the foil could result in participants falsely recognizing the foil pair as the target which they previously learned. Nonetheless, significant group differences on the associative memory measures (i.e., discriminability and false alarm rate) indicate that our findings cannot completely account for by the familiarity to particular studied items.

With respect to brain morphometry correlation, the results showed that bilateral entorhinal cortex was uniquely related to accuracy of item memory while the left hippocampus was uniquely related to false alarm of associative memory given that the correlations continued to hold after controlling the frontal regions across groups. These findings might further support functional distinction in medial temporal lobe: hippocampus is more involved in contextual memory, or recollection process, whereas

entorhinal cortex is more associated with item memory, or familiarity process (Davachi, Mitchell, & Wagner, 2003; Yonelinas et al., 2007). Such relations were observed only in the MCI group, which indicate the associative memory measures in the present study are sensitive to AD pathology. Furthermore, hit rate of associative recognition in the immediate condition was particularly correlated with bilateral entorhinal cortex and the one in the delayed condition was correlated with right entorhinal cortex. This finding could be explained by previous studies that the familiarity could also influence associative recognition through unitization process in encoding, which was related to perirhinal cortex (Diana, Yonelinas, & Ranganath, 2008; A. Mayes et al., 2007). Additionally, the findings of relations between discriminability and bilateral entorhinal cortex as well as hippocampus may suggest that both regions were functionally related to discriminability of associative recognition.

The MCI group had lower *d'* but more false alarms in both immediate and delayed associative recognition with comparable hit rate to the HC groups, suggesting greater difficulty in distinguishing foil pairs from target pairs in the MCI group relatively to the HC group, which was consistent with Hanseeuw and colleagues findings (Hanseeuw et al., 2011). We also found a lower response bias in the MCI group compared to the HC group; however, both groups obtained higher β values (i.e.,

β > 1), which means that they tended to give a "new" response toward stimulus. Such tendency might result from a greater number of foil pairs compared to target pairs in the associative recognition in the present study. Although the β value might not represent the absolute level of response bias, the MCI group had a significant lower β value, indicating more liberal responses compared to the HC group. It is consistent with previous recognition memory studies in patients with very mild AD (Beth, Budson, Waring, & Ally, 2009; Budson, Wolk, Chong, & Waring, 2006). The relation between response bias and the frontal morphometry across groups is also in line with findings that suggested greater liberal response is related to frontal changes (Huh, Kramer, Gazzaley, & Delis, 2006; Kramer et al., 2005; Swick & Knight, 1999), although neither frontal morphometry nor executive function correlations with response bias were found in our MCI group when analyzing separately from the HC group. On the other hand, the correlation between liberal response bias and episodic memory impairment but not executive tests has been reported in very mild AD patients, and researchers suggested that the liberal bias might be related to disease severity (Budson et al., 2006). Conversely, the negative correlations between bias and entorhinal cortex after controlling frontal regions in the MCI group, which indicated that more conservative bias was associated with poor memory. Further research to examine the role of response bias in memory performance of MCI

individuals would help to clarify the relative contributions of frontal and medial temporal structures related to the response bias in individuals with MCI.

Interestingly, we found a relation between executive function and general discriminability in the MCI group. One explanation is that discrimination between several foils and target pairs requires strategic retrieval process (Cohn & Moscovitch, 2007), which may partially account for the involvement of executive function in associative memory recognition. Despite that, we did not find a significant relation between associative memory measures and morphometric measures in frontal regions in the MCI group. It is likely related to the view that the executive function tests might not be specific to the frontal lobe damage (Alvarez & Emory, 2006; Demakis, 2004). Since we did not obtain functional imaging, it is difficult to investigate the cognitive process and the frontal function related to our task directly. It is also noted that half of the MCI individuals in the present study were classified as a-MCI multiple domain and had deficits in executive function in addition to memory function. Thus, another explanation to the correlation with executive function measures might imply lower executive function aggravated associative memory performance, which is in line with previous study in a-MCI (Chang et al., 2010). Similar finding was also showed increased errors along with memory load in visual paired associate task in a-MCI with subtle executive impairment (Harel et al., 2011).

4.2. Features of Chinese characters contribute to associative recognition in MCI

In respect to false alarm types, the MCI group made more rearranged, orthographically-related, and semantically-related type of false alarm, even after controlling for delayed item memory. As expected, the MCI group had much more rearranged false alarm compared to the HC group in the delayed association. Since the two items in a rearranged pair are both learned items during the studying phase, the participants should retrieve particular associations between items in order to reject the foil correctly (Cohn & Moscovitch, 2007; Yonelinas, 1997). Consequently, to make more rearranged errors indicated that the individuals with MCIs had poor associative memory than healthy controls. The correlation between rearranged errors and the left hippocampus further supported that such performance was related to poor integrity in the medial temporal lobe in the MCI individuals. It is out of expected that the rearranged errors in the delayed condition were not associated with the morphometric measures in the medial temporal lobe, likely resulting from compatible number of errors across conditions in the MCI group.

In addition, the MCI group compared to the HC group, made more orthographically-related errors in the delayed condition. Previous studies have suggested that orthography characters shared linguistic information (i.e. meaning of radicals) in addition to visual similarity (Lai, 2008; Lin, 2010); namely,

orthographically-related characters obtained both perceptual and conceptual information similar to the original. It is possible that such similarity gives rise to make errors easier in individuals with MCI whose associative memory was vulnerable. Previously, Newsome, Duarte, and Barense (2012) presented that highly perceptual similar features interfered with visual discrimination task in individuals with MCI according to their assumption of poor integrity of perirhinal cortex in MCI. It seems plausible that a Chinese character could be seen as a figure; however, we did not find association between orthographically-related false alarm and medial temporal ROIs in the present study. Additionally, it is noted that orthographically-related effect was obtained across groups. Thus, the utility of the orthographically-related errors in early detection of AD requires future examination. Some unexpected positive correlations with morphometric measures might also reflect response variation in participants.

Importantly, a higher number of semantically-related false alarms in the MCI group were noted, which might imply vulnerable semantic system in MCI individuals. The semantically-related materials in present study were selected by the similar meaning of characters which assumed that had been stored in the semantic system. The concepts in the semantic system could represent as nodes and connect with each other; consequently, one concept is activated as another related concept is processed

(Collins & Loftus, 1975). Following this postulate, it might be difficulty in discriminating between concepts which shared similar meaning if one's knowledge system was not well organized as usual; consequently, it could be possible that participants made more semantically-related false alarms even though foil characters overall were perceptual dissimilar to the original one. Though semantic knowledge was generally represented in the neocortex, it was mediated by networks consist of anterior and lateral temporal cortex and ventral-lateral prefrontal cortex (Levy, Bayley, & Squire, 2004; Moscovitch et al., 2005). Accordingly, it might indicate that the individuals with MCI had pathological changes beyond medial temporal structures.

4.3. The role of frontal function in the word association task

The morphometric measures in frontal regions correlated with the associative memory variables in the present study indicate that the frontal function might play a role in the verbal paired memory. Table 19 summarizes the correlational findings of the frontal regions and the associative memory variables for all participants across groups. The significant correlations were found in areas of right ventrolateral prefrontal cortex (VLPFC; i.e., the frontal operculum and the lateral orbital frontal cortex) and bilateral dorsolateral prefrontal cortex (DLPFC; i.e., the caudal and rostral middle frontal as well as the superior frontal regions). Although the area in our superior frontal ROI extended to the paracentral sulcus (Desikan et al., 2006), the

anterior lateral portion of this ROI also includes a part of DLPFC.

In this study, we found that the right DLPFC and the right frontal pole were significant related to false alarm rate and discriminability generally; the right VLPFC and frontal pole as well as bilateral DLPFC were further correlated with the discriminability in the delayed condition. According to previous studies (Stuss, 2011; Wagner, Maril, Bjork, & Schacter, 2001), the right lateral frontal regions are responsible for monitoring process while the left one contributes to response set establishment when performing a task. The lateral orbital frontal region is also related to behavioral regulation ability; the frontal poles contribute to the integrative function and executive capacity (Stuss, 2011). Thus, the findings indicate the involvement of executive control process in associative recognition. It could also reflect the characteristics of our task that the Chinese characters are paired arbitrarily and are examined intentionally. Accordingly, the control process might have influence on discriminating target pairs from foils in the associative recognition. The abovementioned findings might also explain the relations between the executive function and associative memory performance in the MCI group. It is in line with literatures which have suggested the role of right DLPFC and the frontal pole in retrieving associative information (Cabeza, Locantore, & Anderson, 2003; Nagel, Schumacher, Goebel, & D'Esposito, 2008) as well as left DLPFC in associative

recognition (Achim & Lepage, 2005).

On the other hand, the right frontal pole, left superior frontal, right DLPFC, and bilateral VLPFC were correlated with different false alarm types (see summary in Table 20). It was noted that only semantically-related false alarm were correlated with left inferior frontal region, which has been found to be related with semantic information retrieval (Ricci et al., 1999; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997) and semantic processing of Chinese characters (Wu, Ho, & Chen, 2012). The various frontal regions correlated with different error types might also imply different neural correlates of conceptual and perceptual false alarms as previous finding based on item recognition task (Garoff-Eaton, Kensinger, & Schacter, 2007). However, the present findings did not find consistent correlation among error types between the immediate and delayed conditions. Since the number of trials in each false alarm type was relatively small, it might be difficult to apply results from previous studies to the current findings concerning performance variation.

4.4. Comparison between the modified recognition and the original version of the Verbal Paired Associate subtest of the WMS-III

The finding of modified recognition on the Verbal PA subtest of the WMS-III with greater effect in the MCI group indicate that additional foils other than novel type are valuable with significant group difference. The discrepancy of accuracy

score between the two version recognition tests may be explained by overestimated performance on the associative recognition in original format. It is consistent with criticism raised from previous studies indicating that ceiling effects in the original WMS-III Verbal PA may restrict the utility of memory assessment (Riley & Zellinger, 2000; Uttl et al., 2002). According to the cue-recall format in learning and delayed recall condition, it is difficult to control item memory, and the participants might perform the recognition task based on the cued items in the delayed cued recall condition. Consequently, more variances in the performance in the MCI group might explain that no significant interaction between group and test version was found. Though our preliminary finding provides clear evidence for revising the standardized version of the test, future research is needed to examine its clinical utility or to refine the task modification in order to improve the reliability of the measure.

4.5. Implication in early detection of AD

The findings of verbal associative memory deficits, especially semantically-related errors, in individuals with MCI correspond to structural changes in left hippocampus suggest the present task is sensitive to AD pathology. This is consistent with the view that paired associate learning is good indicator in early identifying AD (G. Lowndes & Savage, 2007). To our knowledge, this study is the first research applied different features of Chinese characters to investigate how

Chinese speakers with MCI perform the associative memory. Although two studies examined associative memory in Chinese individuals with MCI were noted, one paradigm used visuospatial stimuli (H. M. Wang et al., 2013) and the other one was similar to the Verbal PA subtest of the WMS-III (P. Wang, Li, Li, & Zhang, 2013).

On the other hand, semantic memory decline has been found in individuals with AD in evidence of difficulty in tasks related to picture naming, category fluency, word knowledge, and picture matching, suggesting degradation of semantic storage (Hodges et al., 1992; Huff, Corkin, & Growdon, 1986; Martin & Fedio, 1983; Salmon, Butters, & Chan, 1999). Similar findings have also been obtained in MCI individuals (Adlam et al., 2006; Barbeau et al., 2012; Joubert et al., 2010). Although the present finding did not show worse semantic fluency in the MCI group, elevated semantically-related false alarm in associative memory might be in accord with the view of early semantic system disruptions. Combination with associative and semantic memory in the word association task might provide greater clinical application of examining memory impairments in patients with limbic stage of AD pathology (Didic et al., 2011).

4.6. Limitations

There are some limitations in the present study. First, the sample size is relative small, large sample is needed to obtain more reliable results. Second, due to high

heterogeneity and small sample size in the MCI group, it may not be differentiated associative memory performances from different type of MCI in the present study. Third, the HC group might include individuals with subjective cognitive decline (SCD). Studies have reported that individuals with SCD might have characteristic difference from those without SCD, such as poor psychological well-being, depressive symptoms, and increased risk for cognitive decline (Benito-Leon, Mitchell, Vega, & Bermejo-Pareja, 2010; Glodzik-Sobanska et al., 2007). However, no significant group difference in GDS score was found, and such contamination should be minimal. Fourth, due to lack of validated indicators to support the material characteristics, such as association strength between Chinese characters, it should be cautious about applying the present findings to other verbal materials. Fifth, the present study is cross-sectional in design, and the predictive power of the associative memory measure for AD conversion rate of the current sample is still pending. A followed-up study is underway to longitudinally follow these participants' outcome.

4.7. Conclusion and future research

Despite these limitations, the current study demonstrated that associative memory impairment in MCI could be dissociated from item memory. The finding suggested that worse associative memory might result in problems of target discrimination in individuals with MCI. The false alarm rate and discriminability in

associative recognition were highly corresponded to the regions related to early AD pathology and the involvement of executive control was also implicated. In addition, the word association task in the present study through unique features of Chinese character further supported early semantic system collapsed in MCI. Thus, it would be beneficial to use the present task to investigate early cognitive changes related to AD neuropathology in mandarin speaking populations. Moreover, the preliminary finding about modified recognition of the Verbal PA subtest of the WMS-III implicates overestimated associative recognition performance in the original test, and different variant foils may improve the ability to examine paired learning in individuals with MCI. Future study is needed to investigate the clinical application of the word association task and modified recognition of the Verbal PA subtest of the WMS-III to support the role in AD prediction.

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Tables

Table 1

Demographic & Clinical Characteristic Data

	MCI (n=22)	*HC (n=25)*	t/χ^2	*p*	*Cohen's d*
Age	73.77 (7.70)	70.68 (5.45)	1.57	.125	-
Education	12.50 (2.92)	13.68 (2.87)	-1.40	.170	-
Gender[a] , % male	45.50	40.00	0.14	.706	-
GDS	3.55 (3.74)	3.28 (2.96)	0.27	.787	-
MABP	101.36 (13.13)	92.57 (11.56)	2.44	.019*	0.71
FHS-Stroke risk, %	15.18 (9.79)	11.92 (9.72)	1.15	.258	-
CDR-SB[b]	1.27 (1.22)	0.59 (0.49)	2.45	.021*	0.72
ADL from family[b]	99.55 (2.13)	100.00 (0.00)	-1.00	.329	-
IADL from family[b]	7.32 (0.95)	7.70 (0.56)	-1.62	.114	-

Note. GDS, Geriatric Depression Scale; MABP, mean arterial blood pressure; FHS-Stroke risk, Framingham Heart Study 10 years stroke risk probability; CDR-SB, Clinical Dementia Rating-Sum of Boxes; ADL, activities of daily living scored by Barthel Scale; IADL, Lawton's Instrumental Activities of Daily Living Scale.

[a]Chi - square Test. [b]Only 23 HC data were obtained and analyzed.

* $p < .05$

Table 2

Neuropsychological Performance (Raw Scores) of the MCI and HC Groups

	MCI(n=21)	*HC(n=23)*	*t*	*p*	*d*[a]
Est. FSIQ[b]	105.97 (9.85)	115.71 (10.46)	-3.17	.003	-
Language					
Vocabulary	40.10 (8.82)	46.17 (8.85)	-2.28	.028	-
Boston Naming Test	27.14 (3.28)	28.26 (1.48)	-1.44	.163	-
Attention					
Digit Span-FS	7.24 (1.26)	8.00 (0.80)	-2.37	.024	-
Spatial Span- FS	5.29 (1.10)	5.96 (0.88)	-2.22	.032	-
Executive function					
Working Memory Index[c]	27.05 (5.73)	33.70 (5.27)	-4.01	<.001*	1.21
Digit Span-BS	4.19 (0.93)	5.26 (1.29)	-3.14	.003	-
Spatial Span- BS	4.86 (1.01)	5.57 (1.16)	-2.15	.038	-
MCST					
Category	3.62 (2.20)	5.74 (1.29)	-3.85	.001*	1.16
Perseverative error	8.81 (11.03)	2.91 (3.27)	2.36	.027	-
Non-Perseverative error	8.05 (4.35)	5.65 (2.99)	2.14	.038	-
Unique error	2.48 (2.79)	0.61 (1.27)	2.82	.009	-
Color Trails Test (2-1)[d]	57.27 (25.55)	53.23 (28.40)	0.49	.624	-
Matrix Reasoning	9.90 (4.94)	14.78 (5.70)	-3.02	.004	-
Similarities	16.62 (6.28)	19.39 (6.35)	-1.45	.153	-
DF-Switching	4.38 (2.18)	6.83 (2.15)	-3.75	.001*	1.13
Semantic Fluency-animal	14.05 (3.01)	17.70 (4.03)	-3.38	.002	-
Visuomotor					
Color Trails Test-1	74.52 (40.30)	47.22 (14.95)	2.93	.007	-
Digit-Symbol Substitution	48.76 (16.30)	61.70 (15.80)	-2.67	.011	-
Visual spatial					
Block Design	29.00 (9.09)	37.39 (7.70)	-3.31	.002	-

(continued)

Learning and Memory					
Logical Memory					
Immediate recall	20.95 (9.38)	38.30 (9.01)	-6.25	<.001*	1.89
Delayed recall	11.14 (7.02)	24.04 (7.87)	-5.72	<.001*	1.73
Delayed recognition	20.90 (4.09)	25.09 (2.83)	-3.91	<.001*	1.18
Visual Reproduction					
Immediate recall	61.33 (13.10)	79.43 (11.05)	-4.97	<.001*	1.50
Delayed recall	31.24 (21.49)	58.52 (19.32)	-4.44	<.001*	1.34
Delayed recognition	38.33 (6.88)	43.70 (2.06)	-3.44	.002	-
Verbal Paired Associate					
Immediate recall	9.10 (6.86)	18.09 (5.24)	-4.91	<.001*	1.48
Delayed recall	2.71 (2.35)	6.39 (1.83)	-5.82	<.001*	1.76
Delayed recognition	21.71 (2.80)	23.52 (0.79)	-2.86	.009	-
Visual Paired Associate					
Immediate recall	7.10 (3.86)	12.52 (2.78)	-5.39	<.001*	1.63
Delayed recall	3.52 (2.25)	5.65 (0.78)	-4.12	<.001*	1.24

Note. Est. FSIQ, estimated full scale IQ; MCST, Modified Card Sorting Test; Digit Span-FS, Digit Span-Forward Span; Digit Span-BS, Digit Span-Backward Span; Spatial Span-FS, Spatial Span-Forward Span; Spatial Span-BS, Spatial Span-Backward Span; DF-switching. Design Fluency-switching condition.

[a] Cohen's *d*. [b] Standard score is presented, which mean value is 100 and the standard deviation is 15. [c]consist of the Arithmetic and the Digit Span subtests of the WAIS-III. [d]Time difference was calculated from the Color Trail Test Part 2 minus Part 1.

*$p < .0016$, based on Bonferroni correction

Table 3

Raw Mean Volume for Hippocampus and Cortical Thickness for Frontal, Temporal, and Cingulate Regions by Group

	MCI(n=21) (mean S.D.)	*HC(n=23)* (mean S.D.)	*t*	*p*	*d*
Hippocampus (mm^3)					
Left	3286.00 (507.36)	3532.78 (394.07)	-1.86	.071	-
Right	3339.10 (612.83)	3720.65 (501.02)	-2.35	.024*	0.71
Parahippocampal (mm)					
Left	2.45 (0.36)	2.64 (0.32)	-1.72	.093	-
Right	2.46 (0.26)	2.60 (0.25)	-1.75	.088	-
Entorhinal (mm)					
Left	3.13 (0.33)	3.34 (0.30)	-2.18	.035*	0.66
Right	3.26 (0.48)	3.36 (0.44)	-0.74	.464	-
Frontal pole (mm)					
Left	2.65 (0.22)	2.80 (0.25)	-2.02	.050	-
Right	2.67 (0.17)	2.79 (0.24)	-1.82	.076	-
Caudal middle frontal (mm)					
Left	2.54 (0.14)	2.57 (0.13)	-0.71	.484	-
Right	2.55 (0.14)	2.60 (0.12)	-1.32	.196	-
Rostral middle frontal (mm)					
Left	2.29 (0.08)	2.23 (0.12)	-1.43	.161	-
Right	2.30 (0.09)	2.33 (0.11)	-0.95	.348	-
Lateral orbital frontal (mm)					
Left	2.54 (0.09)	2.63 (0.17)	-2.29	.029*	0.69
Right	2.58 (0.11)	2.60 (0.14)	-0.90	.373	-
Medial orbital frontal (mm)					
Left	2.49 (0.14)	2.55 (0.16)	-1.36	.182	-
Right	2.48 (0.18)	2.49 (0.20)	-0.28	.784	-
Superior frontal (mm)					
Left	2.72 (0.10)	2.78 (0.11)	-1.78	.082	-
Right	2.69 (0.12)	2.73 (0.13)	-1.01	.319	-
Pars orbitalis (mm)					
Left	2.53 (0.12)	2.58 (0.22)	-0.99	.328	-
Right	2.63 (0.16)	2.63 (0.17)	-0.12	.903	-

(continued)

Frontal operculum (mm)					
Left	2.47 (0.26)	2.49 (0.11)	-0.72	.478	-
Right	2.48 (0.12)	2.51 (0.11)	-1.21	.233	-
Anterior cingulate (mm)					
Left	2.72 (0.19)	2.78 (0.24)	-0.88	.392	-
Right	2.78 (0.23)	2.74 (0.20)	0.62	.541	-
Posterior cingulate (mm)					
Left	2.45 (0.20)	2.49 (0.17)	-0.63	.531	-
Right	2.36 (0.16)	2.43 (0.17)	-1.32	.193	-

Note. Statistical comparisons for regional morphometric variables controlled for gender effects. For hippocampus, estimated intracranial volume was also included as a covariate.

* $p < .05$

Table 4

Performance on the Word Association Task between Groups

	MCI (n = 22)	*HC (n = 25)*	*Statistics & p-value*
Number of total learning	3.55 (0.51)	3.20 (0.41)	$t_{(40.20)} = 2.54$, $p = .015^{*}$
Item memory			
ACC -immed	87.70 (8.85)	91.75 (6.74)	$F_{(1, 90)} = 3.22$, $p = .076$
ACC -delayed	80.54 (12.08)	91.13 (7.48)	$F_{(1, 90)} = 16.51$, $p < .001^{***}$
Associative memory			
d'- immed[a]	1.93 (0.60)	2.54 (0.42)	-
d'- delayed[a]	1.48 (0.63)	2.22 (0.62)	-
β - immed[a]	1.44 (1.46)	2.20 (1.96)	-
β - delayed[a]	1.25 (1.41)	2.48 (1.25)	-
Hit –immed[a]	82.39 (19.92)	86.00 (14.58)	-
Hit-delayed[a]	76.71 (23.56)	79.50 (17.26)	-
Total FA-immed	20.34 (14.91)	8.80 (6.30)	$F_{(1, 90)} = 9.80$, $p = .002^{**}$
Total FA-delayed	28.52 (18.17)	11.20 (8.57)	$F_{(1, 90)} = 22.08$, $p < .001^{***}$

Note. ACC, accuracy; immed, immediate; FA, false alarm.

[a] without group by time interaction.

$^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$

Table 5

Correlation Coefficients between Word Association Task Performances and Brain Morphometry for all Participants

		Item recognition		Immediate association				Delayed association			
		Immediate	Delayed	Hit	False alarm	*d'*	*β*	Hit	False alarm	*d'*	*β*
Frontal lobe											
Frontal pole	Lt	.12	.10	.08	-.07	.18	.85	.13	-.06	.18	-.00
	Rt	.21	.11	-.14	-.33*	.20	.25	.01	-.35*	.34*	.19
Caudal middle	Lt	.42**	.36*	.01	-.20	.20	.25	.20	-.22	.33*	-.01
	Rt	.21	.21	-.25	-.36*	.09	.28	-.05	-.36*	.27	.14
Rostral middle	Lt	.25	.19	.01	-.27	.28	.22	.18	-.25	.37*	.09
	Rt	.39**	.34*	-.01	-.20	.19	.16	.15	-.31*	.39**	.08
Lateral orbital	Lt	.11	.13	-.17	-.23	.11	.31*	-.02	-.25	.26	.27
	Rt	.12	.12	.04	-.12	.17	.04	.11	-.16	.31*	.27
Medial orbital	Lt	.21	.13	-.04	-.14	.15	.23	.11	-.12	.24	.14
	Rt	.06	.01	.00	.14	-.08	.03	.15	.08	.12	.03
Superior frontal	Lt	.27	.23	-.01	-.26	.23	.21	.11	-.29	.34*	.09
	Rt	.29	.21	-.14	-.32*	.17	.23	-.01	-.33*	.26	.10
Pars orbitalis	Lt	.01	-.03	-.12	-.19	.05	.10	.02	-.19	.22	.19
	Rt	.30	.23	.26	.05	.19	-.13	.25	.03	.21	.03
Operculum	Lt	.12	.08	-.22	-.23	.03	.21	-.10	-.28	.22	.29
	Rt	.28	.33*	-.07	-.24	.22	.25	.14	-.36*	.47**	.23

(continued)

Cingulate cortex											
Anterior	Lt	.09	.00	-.16	-.20	.07	.23	-.06	-.22	.17	.21
	Rt	-.01	.01	-.05	.14	-.09	.06	.05	-.03	.09	-.04
Posterior	Lt	.19	.14	-.03	-.07	.06	.05	-.07	-.27	.20	.16
	Rt	.15	.15	-.11	-.10	.01	.08	.02	-.25	.25	.10
Temporal lobe											
Parahippocampal	Lt	.30	.32*	.20	-.06	.21	-.09	.19	-.09	.23	-.01
	Rt	.21	.30*	.18	-.04	.20	-.10	.20	-.09	.27	.03
Entorhinal	Lt	.47**	.44**	.32*	-.25	.50**	.03	.29	-.17	.37*	-.01
	Rt	.41**	.42**	.54**	-.05	.50**	-.25	.42**	.02	.32*	-.18
Hippocampus	Lt	.23	.32*	-.01	-.47**	.38*	.21	.04	-.41**	.37*	.13
	Rt	.19	.29	.13	-.25	.35*	.11	.09	-.29	.33*	.15

Note. N= 44. Lt, Left; Rt, Right.

* $p < .05$; ** $p < .01$

Table 6

Partial Correlation Coefficients Controlling the Frontal Regions[a] *between Word Association Task Performances and Brain Morphometry for All Participants*

		Item recognition		Immediate association				Delayed association			
		Immediate	Delayed	Hit	False alarm	*d'*	*β*	Hit	False alarm	*d'*	*β*
Cingulate cortex											
Anterior	Lt	-.07	-.15	-.14	-.06	-.05	.13	-.13	-.06	-.04	.15
	Rt	-.07	-.04	-.04	.21	-.15	.10	.03	.03	.01	-.07
Posterior	Lt	.07	.04	.00	.06	-.04	-.07	-.13	-.15	.04	.10
	Rt	-.03	.00	-.08	.08	-.15	-.08	-.05	-.08	.03	.01
Temporal lobe											
Parahippocampal	Lt	.21	.25	.24	.04	.15	-.20	.17	.03	.11	-.07
	Rt	.11	.23	.22	.08	.13	-.21	.18	.04	.14	-.03
Entorhinal	Lt	.40**	.38*	.38*	-.16	.46**	-.07	.27	-.05	.26	-.08
	Rt	.38*	.39**	.56***	.01	.48**	-.32*	.41**	.10	.27	-.22
Hippocampus	Lt	.15	.26	.01	-.41**	.34*	.14	.01	-.34*	.28	.09
	Rt	.14	.26	.15	-.21	.32*	.06	.07	-.25	.30	.13

Note. N= 44; Lt, Left; Rt, Right.

[a] bilateral frontal pole, bilateral middle frontal, bilateral superior frontal, bilateral lateral orbital frontal, and right frontal operculum cortex.

*$p < .05$; **$p < .01$; ***$p < .001$

Table 7

Correlation Coefficients between Word Association Task Performances and Brain Morphometry in the MCI Group

		Item recognition						Immediate association				Delayed association			
		Immediate	Delayed	Hit	False alarm	*d'*	*β*	Hit	False alarm	*d'*	*β*				
Frontal lobe															
Frontal pole	Lt	-.20	-.21	-.10	.14	-.22	-.04	.00	.24	-.22	.03				
	Rt	.06	.11	-.24	-.29	-.02	.11	-.18	-.33	.15	.16				
Caudal middle	Lt	.55**	.61**	-.01	-.19	.13	.22	.19	-.23	.33	-.21				
	Rt	.22	.28	-.34	-.37	-.07	.09	-.28	-.42	.14	.25				
Rostral middle	Lt	.37	.28	.07	-.21	.21	-.03	.08	-.13	.12	-.10				
	Rt	.42	.45*	-.15	-.20	-.02	.12	-.14	-.38	.18	.12				
Lateral orbital	Lt	.01	.02	-.13	.07	-.31	-.32	-.12	.03	-.16	.10				
	Rt	-.07	-.03	.00	-.01	-.05	-.20	.06	.04	-.01	-.11				
Medial orbital	Lt	.20	.15	.13	.10	-.04	-.31	.10	.09	-.03	-.12				
	Rt	-.16	-.08	.05	.37	-.35	-.39	.01	.28	-.26	-.06				
Superior frontal	Lt	.28	.29	-.14	-.27	.04	.20	.00	-.21	.11	-.09				
	Rt	.43	.41	-.22	-.40	.07	.14	-.19	-.38	.13	.09				
Pars orbitalis	Lt	-.18	-.11	-.07	.05	-.24	-.27	.04	.10	-.07	-.07				
	Rt	.32	.16	.30	.22	.04	-.29	.15	.21	-.16	-.25				
Operculum	Lt	.05	.05	-.34	-.23	-.16	.10	-.33	-.24	-.06	.33				
	Rt	.18	.25	-.27	-.16	-.12	.19	-.16	-.37	.20	.17				

(continued)

Cingulate cortex											
Anterior	Lt	.02	.05	-.04	-.09	.00	-.08	-.12	-.04	-.07	.11
	Rt	-.01	.14	.08	.23	-.09	-.17	-.03	-.06	.11	.11
Posterior	Lt	.03	.06	-.12	.05	-.19	-.06	-.23	-.24	.00	.20
	Rt	.09	.18	-.15	.09	-.32	-.19	-.15	-.17	.03	.16
Temporal lobe											
Parahippocampal	Lt	.27	.37	.20	.02	.14	-.14	.16	.07	-.01	-.26
	Rt	.10	.23	.12	.10	.02	-.15	.18	.13	.01	-.21
Entorhinal	Lt	.55*	.49*	.56**	-.11	.61**	-.25	.39	.10	.15	-.46*
	Rt	.46*	.52*	.66**	.02	.58**	-.45*	.50*	.15	.26	-.49*
Hippocampus	Lt	.43	.45*	.00	-.53*	.46*	.09	-.01	-.50*	.48*	.09
	Rt	.28	.31	.13	-.17	.25	-.08	.13	-.23	.34	-.06

Note. N= 21; Lt, Left; Rt, Right.

* $p < .05$; ** $p < .01$

Table 8

Partial Correlation Coefficients Controlling the Frontal Regions[a] *between Word Association Task Performances and Brain Morphometry for the MCI Group*

		Item recognition		Immediate association				Delayed association			
		Immediate	Delayed	Hit	False alarm	*d'*	*β*	Hit	False alarm	*d'*	*β*
Cingulate cortex											
Anterior	Lt	-.06	-.04	-.01	-.07	.03	-.09	-.12	.00	-.09	.12
	Rt	.05	.21	.06	.22	-.11	-.16	-.03	-.09	.12	.11
Posterior	Lt	-.08	-.07	-.08	.08	-.17	-.08	-.24	-.20	-.03	.21
	Rt	-.06	.02	-.11	.15	-.30	-.23	-.16	-.12	-.01	.18
Temporal lobe											
Parahippocampal	Lt	.20	.30	.25	.05	.18	-.16	.16	.12	-.03	-.27
	Rt	-.02	.11	.18	.14	.07	-.18	.19	.20	-.02	-.22
Entorhinal	Lt	.51*	.44	.61**	-.10	.66**	-.27	.40	.14	.14	-.47*
	Rt	.49*	.55*	.67**	.02	.59**	-.45*	.50*	.15	.26	-.49*
Hippocampus	Lt	.40	.43	.02	-.52*	.48*	.09	-.01	-.49**	.48**	.09
	Rt	.26	.29	.14	-.16	.27	-.09	.13	-.22	.33	-.05

Note. N= 21; Lt, Left; Rt, Right.

[a] left frontal pole, left lateral orbital frontal, left caudal middle frontal, and right rostral middle frontal cortex.

* $p < .05$; ** $p < .01$

Table 9

Correlation Coefficients between Word Association Task Performances and Brain Morphometry for the HC Group

		Item recognition		Immediate association				Delayed association			
		Immediate	Delayed	Hit	False alarm	*d'*	*β*	Hit	False alarm	*d'*	*β*
Frontal lobe											
Frontal pole	Lt	.28	.14	.21	-.03	.31	-.03	.26	-.07	.22	-.15
	Rt	.23	-.17	-.13	-.27	.17	.24	.15	-.26	.32	.12
Caudal middle	Lt	.24	-.01	.01	-.16	.23	.24	.21	-.16	.32	.09
	Rt	.09	-.11	-.20	-.24	.09	.38	.20	-.11	.26	-.03
Rostral middle	Lt	.08	-.07	-.10	-.29	.22	.28	.26	-.27	.43*	.10
	Rt	.34	.19	.10	-.14	.31	.14	.40	-.22	.50*	-.00
Lateral orbital	Lt	.03	-.08	-.32	-.36	.09	.46*	.02	-.30	.25	.25
	Rt	.21	.17	.05	-.16	.28	.10	.16	-.35	.45*	.41
Medial orbital	Lt	.13	-.10	-.28	-.37	.18	.49*	.11	-.22	.30	.21
	Rt	.26	.07	-.06	-.10	.14	.26	.28	-.10	.37	.06
Superior frontal	Lt	.14	-.09	.07	-.05	.20	.13	.22	-.20	.35	.10
	Rt	.08	-.16	-.11	-.18	.15	.25	.15	-.24	.28	.04
Pars orbitalis	Lt	.06	-.16	-.20	-.44*	.13	.19	.01	-.44*	.29	.25
	Rt	.29	.41	.22	-.21	.42*	-.05	.35	-.25	.52*	.20
Operculum	Lt	.13	.03	-.16	-.26	.09	.24	.07	-.40	.34	.24
	Rt	.30	.36	.11	-.26	.47*	.24	.43*	-.29	.62**	.20

(continued)

Cingulate cortex											
Anterior	Lt	.09	-.23	-.32	-.32	.02	.36	-.03	-.44*	.24	.22
	Rt	.06	-.05	-.23	-.17	.00	.27	.14	-.19	.20	-.11
Posterior	Lt	.37	.21	.08	-.25	.36	.10	.14	-.34	.35	.10
	Rt	.10	-.12	-.12	-.27	.18	.20	.20	-.22	.31	-.03
Temporal lobe											
Parahippocampal	Lt	.20	.01	.15	.13	.04	-.17	.25	.01	.25	.07
	Rt	.21	.19	.20	.05	.18	-.17	.24	-.12	.32	.10
Entorhinal	Lt	.25	.13	-.03	-.21	.17	.11	.21	-.24	.36	.17
	Rt	.32	.29	.35	-.03	.43*	-.17	.32	-.01	.35	-.00
Hippocampus	Lt	-.26	-.23	-.13	-.11	.03	.23	.10	.09	.07	.06
	Rt	-.18	-.12	.06	-.02	.16	.14	.04	.05	.08	.19

Note. N= 23; Lt, Left; Rt, Right.

* $p < .05$; ** $p < .01$

Table 10

Partial Correlation Coefficients Controlling the Frontal Regions[a] *between Word Association Task Performances and Brain Morphometry for the HC Group*

		Item recognition		Immediate association				Delayed association			
		Immediate	Delayed	Hit	False alarm	*d'*	*β*	Hit	False alarm	*d'*	*β*
Cingulate cortex											
Anterior	Lt	-.10	-.41	-.39	-.13	-.31	.25	-.31	-.29	-.18	.10
	Rt	-.09	-.14	-.24	.02	-.24	.16	-.01	.01	-.11	-.28
Posterior	Lt	.31	.18	.11	-.15	.27	.00	.03	-.23	.19	.02
	Rt	-.04	-.21	-.11	-.11	.00	.07	.06	-.05	.06	-.17
Temporal lobe											
Parahippocampal	Lt	.13	-.03	.17	.26	-.07	-.28	.18	.13	.12	.01
	Rt	.12	.16	.24	.22	.05	-.33	.14	.03	.14	.01
Entorhinal	Lt	.16	.08	-.01	-.06	.00	-.02	.09	-.08	.15	.07
	Rt	.26	.27	.39	.10	.35	-.29	.25	.13	.21	-.09
Hippocampus	Lt	-.36	-.28	-.12	-.01	-.08	.16	.01	.23	-.11	-.01
	Rt	-.19	-.13	.06	-.02	.16	.14	.03	.07	.07	.19

Note. N= 23; Lt, Left; Rt, Right

[a] left frontal pole, bilateral rostral middle frontal, bilateral lateral orbital frontal, left medial orbital frontal, bilateral pars orbitalis, right frontal operculum.

$^{*}p < .05$; $^{**}p < .01$

Table 11

Correlation Coefficients between False Alarm Type of the Word Association Task and Morphometry for All Participants

		Immediate association					Delayed association				
		Sem	Pho	Ort	Re	No	Sem	Pho	Ort	Re	No
Frontal											
Frontal pole	Lt	-.10	-.04	-.07	-.04	-.05	-.02	-.05	-.11	-.05	.00
	Rt	-.42**	-.20	-.43**	-.18	-.10	-.27	-.33*	-.45**	-.24	-.02
Caudal middle	Lt	-.28	-.16	-.15	-.15	-.01	-.20	-.26	-.17	-.21	.21
	Rt	-.34*	-.28	-.39**	-.27	-.08	-.38*	-.27	-.28	-.35*	.12
Rostral middle	Lt	-.35*	-.24	-.25	-.18	.00	-.29	-.21	-.21	-.19	.10
	Rt	-.39**	-.14	-.26	-.08	.06	-.36*	-.23	-.29	-.25	.13
Lateral orbital	Lt	-.29	-.09	-.29	-.17	-.01	-.22	-.15	-.28	-.24	.07
	Rt	-.29	-.07	-.18	-.01	.11	-.16	-.06	-.22	-.14	.05
Medial orbital	Lt	-.12	-.08	-.17	-.10	-.07	-.10	-.01	-.11	-.16	-.02
	Rt	.04	.07	.04	.23	.07	.13	.20	-.07	.05	.09
Superior frontal	Lt	-.30	-.23	-.32*	-.14	-.07	-.32*	-.27	-.23	-.24	.10
	Rt	-.39**	-.24	-.39**	-.20	-.05	-.39**	-.25	-.27	-.27	.05
Pars orbitalis	Lt	-.22	-.19	-.14	-.16	.05	-.15	-.14	-.04	-.29	.10
	Rt	-.02	-.04	.22	-.01	.17	.03	.05	.13	-.07	.11
Operculum	Lt	-.41**	-.05	-.21	-.21	.11	-.31*	-.25	-.23	-.25	.15
	Rt	-.45**	-.11	-.29	-.16	.18	-.36*	-.25	-.39**	-.32*	.29

(continued)

Cingulate cortex											
Anterior	Lt	-.15	-.10	-.21	-.15	-.25	-.16	-.13	-.21	-.22	-.07
	Rt	.10	.07	.17	.13	-.02	.05	-.05	-.08	-.04	-.02
Posterior	Lt	-.15	-.05	-.14	-.02	.12	-.18	-.21	-.34*	-.26	.24
	Rt	-.25	-.05	-.20	-.03	.20	-.22	-.12	-.36*	-.22	.23
Temporal											
Parahippocampal	Lt	-.12	-.09	-.07	.02	-.09	-.09	.00	-.19	-.04	-.09
	Rt	-.08	.02	-.03	-.05	-.03	-.04	.03	-.23	-.07	-.04
Entorhinal	Lt	-.39**	-.14	-.09	-.22	-.23	-.19	-.20	-.08	-.13	-.13
	Rt	-.14	-.09	.08	-.01	-.10	-.05	-.04	.08	.08	-.10
Hippocampus	Lt	-.35*	-.51**	-.18	-.43**	-.41**	-.42**	-.41**	-.29	-.29	-.41**
	Rt	-.27	-.30*	.02	-.25	-.19	-.28	-.27	-.31*	-.17	-.28

Note. N = 44; Lt, Left; Rt, Right; Sem, semantically-related; Pho, phonologically-related; Ort, orthographically-related; Re, rearranged; No, novel.

*$p < .05$; **$p < .01$

Table 12

Partial Correlation Coefficients Controlling the Frontal Regions[a] *between False Alarm Type of the Word Association Task and Morphometric for All Participants*

		Immediate association					Delayed association				
		Sem	Pho	Ort	Re	No	Sem	Pho	Ort	Re	No
Cingulate cortex											
Anterior	Lt	.07	.00	-.05	-.06	-.28	.02	.00	-.06	-.09	-.15
	Rt	.21	.12	.26	.18	-.02	.14	.00	-.02	.02	-.05
Posterior	Lt	.02	.04	.00	.07	.13	-.05	-.11	-.24	-.16	.21
	Rt	-.03	.07	-.01	.10	.24	-.03	.03	-.22	-.07	.19
Temporal											
Parahippocampal	Lt	.01	-.03	.05	.09	-.10	.03	.10	-.10	.06	-.13
	Rt	.09	.10	.12	.03	-.03	.11	.14	-.13	.04	-.09
Entorhinal	Lt	-.28	-.07	.05	-.15	-.25	-.07	-.11	.06	-.02	-.19
	Rt	-.08	-.06	.15	.03	-.11	.01	.00	.14	.13	-.12
Hippocampus	Lt	-.25	-.48**	-.08	-.39**	-.43**	-.35*	-.35*	-.21	-.22	-.47**
	Rt	-.22	-.28	.09	-.22	-.20	-.24	-.24	-.28	-.13	-.31*

Note. N = 44; Lt, Left; Rt, Right; Sem, semantically-related; Pho, phonologically-realted; Ort, orthographically-related; Re, rearranged; No, novel.

[a] bilateral frontal pole, right caudal middle frontal, bilateral rostral middle frontal, left lateral orbital frontal, bilateral superior frontal, bilateral frontal operculum.

* $p < .05$; ** $p < .01$; *** $p < .001$

Table 13

Correlation Coefficients between False Alarm Type of the Word Association Task and Morphometry in the MCI Group

		Immediate association					Delayed association				
		Sem	Pho	Ort	Re	No	Sem	Pho	Ort	Re	No
Frontal											
Frontal pole	Lt	.17	.23	.13	.02	.03	.36	.21	.05	.20	.12
	Rt	-.36	-.27	-.43	-.10	-.06	-.20	-.34	-.43	-.27	.07
Caudal middle	Lt	-.35	.03	-.20	-.20	.02	-.22	-.32	-.12	-.26	.34
	Rt	-.38	-.21	-.43	-.32	-.04	-.42	-.32	-.26	-.53*	.24
Rostral middle	Lt	-.48*	-.02	-.16	-.19	.11	-.26	-.21	-.04	-.03	.27
	Rt	-.47*	-.03	-.28	-.11	.16	-.40	-.30	-.33	-.38	.28
Lateral orbital	Lt	-.18	.17	-.10	.19	.17	.03	.02	.01	-.01	.33
	Rt	-.31	.06	-.29	.19	.28	-.05	.02	.04	.09	.16
Medial orbital	Lt	.16	.02	.10	.11	-.04	.08	.16	.22	-.08	.04
	Rt	.23	.27	.24	.46*	.14	.35	.32	.15	.16	.17
Superior frontal	Lt	-.40	-.07	-.39	-.18	-.02	-.27	-.27	-.05	-.22	.26
	Rt	-.51*	-.20	-.46*	-.32	-.02	-.49*	-.31	-.15	-.43	.14
Pars orbitalis	Lt	-.21	.06	-.19	.28	.19	-.04	.03	.27	.04	.30
	Rt	.09	.17	.17	.22	.28	.12	.16	.24	.20	.18
Operculum	Lt	-.53*	.06	-.24	-.26	.25	-.33	-.17	-.23	-.20	.32
	Rt	-.50*	.04	-.33	-.08	.36	-.35	-.29	-.40	-.41	.52*

(continued)

Cingulate cortex											
Anterior	Lt	.05	-.13	-.07	-.02	-.38	.04	-.08	.00	-.08	-.08
	Rt	.28	.09	.29	.21	-.06	.11	-.10	-.13	-.11	-.06
Posterior	Lt	-.12	.01	-.11	.19	.20	-.15	-.22	-.36	-.23	.35
	Rt	-.17	.14	-.10	.19	.38	-.17	-.07	-.24	-.21	.40
Temporal											
Parahippocampal	Lt	.02	.03	-.12	.12	-.04	.05	.08	-.02	.16	-.05
	Rt	.05	.13	-.01	.13	.05	.19	.16	-.13	.22	.03
Entorhinal	Lt	-.27	-.09	-.06	.02	-.24	-.05	-.17	.19	.35	-.09
	Rt	-.18	-.02	.13	.11	-.11	-.04	-.06	.22	.39	-.11
Hippocampus	Lt	-.37	-.51*	-.27	-.52*	-.47*	-.53*	-.54*	-.31	-.34	-.47*
	Rt	-.25	-.20	.05	-.16	-.16	-.23	-.27	-.26	-.03	-.30

Note. N = 21; Lt, Left; Rt, Right; Sem, semantically-related; Pho, phonologically-related; Ort, orthographically-related; Re, rearranged; No, novel.

*$p < .05$; **$p < .01$

Table 14

Partial Correlation Coefficients Controlling the Frontal Regions[a] *between False Alarm Type of the Word Association Task and Morphometric for the MCI Group*

		Immediate association					Delayed association				
		Sem	Pho	Ort	Re	No	Sem	Pho	Ort	Re	No
Cingulate cortex											
Anterior	Lt	.09	-.13	-.05	-.01	-.40	.06	-.06	.02	-.06	-.12
	Rt	.27	.09	.27	.20	-.04	.09	-.12	-.16	-.14	-.02
Posterior	Lt	.09	-.01	.02	.27	.14	-.04	-.16	-.31	-.12	.22
	Rt	.08	.14	.06	.31	.34	-.04	.03	-.16	-.07	.25
Temporal											
Parahippocampal	Lt	.15	.02	-.05	.16	-.10	.13	.13	.03	.26	-.17
	Rt	.21	.13	.08	.18	-.01	.29	.23	-.07	.34	-.10
Entorhinal	Lt	-.21	-.10	-.01	.04	-.28	.00	-.14	.24	.43	-.19
	Rt	-.20	-.02	.14	.11	-.11	-.04	-.06	.23	.41	-.12
Hippocampus	Lt	-.34	-.52*	-.24	-.51*	-.51*	-.51*	-.53*	-.29	-.32	-.58**
	Rt	-.19	-.21	.11	-.14	-.20	-.19	-.24	-.23	.03	-.41

Note. N = 21; Lt, Left; Rt, Right; Sem, semantically-related; Pho, phonologically-related; Ort, orthographically-related; Re, rearranged; No, novel.

[a] left frontal pole, left lateral orbital frontal, right caudal middle frontal, bilateral rostral middle frontal, right medial orbital frontal, right superior frontal, bilateral frontal operculum.

* $p < .05$; ** $p < .01$

Table 15

Correlation Coefficients between False Alarm Type of the Word Association Task and Morphometry in the HC Group

		Immediate association				Delayed association			
		Sem	Pho	Ort	Re	Sem	Pho	Ort	Re
Frontal									
Frontal pole	Lt	-.34	-.21	-.07	.16	-.22	-.22	.03	.01
	Rt	-.56**	.03	-.40	-.07	-.23	-.27	-.47*	-.06
Caudal middle	Lt	-.14	-.46*	-.01	-.01	-.12	-.13	-.17	-.11
	Rt	-.18	-.29	-.22	-.08	-.18	.00	-.13	-.07
Rostral middle	Lt	-.20	-.48*	-.28	-.05	-.34	-.13	-.28	-.16
	Rt	-.35	-.23	-.20	.07	-.46*	-.07	-.21	-.09
Lateral orbital	Lt	-.42*	-.13	-.34	-.20	-.29	-.13	-.41	-.16
	Rt	-.34	-.16	-.04	-.06	-.34	-.08	-.54**	-.19
Medial orbital	Lt	-.53**	-.10	-.43*	-.16	-.22	-.09	-.42*	-.08
	Rt	-.24	-.19	-.20	.09	-.16	.13	-.43*	.02
Superior frontal	Lt	-.01	-.36	-.08	.10	-.27	-.11	-.30	-.08
	Rt	-.20	-.25	-.28	.02	-.30	-.11	-.44*	-.06
Pars orbitalis	Lt	-.28	-.44*	-.03	-.36	-.27	-.32	-.19	-.42*
	Rt	-.22	-.41*	.38	-.24	-.15	-.14	.03	-.29
Operculum	Lt	-.41	-.12	-.18	-.14	-.50*	-.42*	-.24	-.24
	Rt	-.40	-.25	-.15	-.10	-.45*	-.08	-.33	-.15

(continued)

Cingulate cortex									
Anterior	Lt	-.45*	.03	-.35	-.19	-.54**	-.17	-.50*	-.26
	Rt	-.45*	-.04	-.12	-.05	-.35	-.08	-.20	-.08
Posterior	Lt	-.18	-.08	-.14	-.22	-.25	-.14	-.32	-.26
	Rt	-.35	-.23	-.23	-.10	-.15	-.04	-.49*	-.08
Temporal									
Parahippocampal	Lt	-.24	-.10	.32	.16	.10	.19	-.22	.02
	Rt	-.13	.07	.24	-.02	-.08	.07	-.15	-.12
Entorhinal	Lt	-.55**	.04	.21	-.25	-.04	.03	-.11	-.31
	Rt	.02	-.16	.13	-.04	.19	.15	.01	-.11
Hippocampus	Lt	-.09	-.40	.31	-.11	.27	.18	.11	-.03
	Rt	-.04	-.29	.42*	-.09	.20	.07	.01	.00

Note. N = 23; Lt, Left; Rt, Right; Sem, semantically-related; Pho, phonologically-related; Ort, orthographically-related; Re, rearranged; No, novel.

*$p < .05$; **$p < .01$

Table 16

Partial Correlation Coefficients Controlling the Frontal Regions[a] between False Alarm Type of the Word Association Task and Morphometric for the HC Group

		Immediate association				Delayed association			
		Sem	Pho	Ort	Re	Sem	Pho	Ort	Re
Cingulate cortex									
Anterior	Lt	-.21	.37	-.28	-.16	-.40	-.04	-.34	-.18
	Rt	-.27	.18	.00	.01	-.17	.04	.02	.03
Posterior	Lt	-.01	.05	-.06	-.20	-.12	-.07	-.20	-.21
	Rt	-.13	-.06	-.13	-.05	.09	.09	-.36	.03
Temporal									
Parahippocampal	Lt	-.13	.00	.42	.20	.25	.27	-.11	.09
	Rt	.04	.21	.35	.02	.07	.16	-.01	-.05
Entorhinal	Lt	-.44*	.22	.35	-.22	.16	.13	.08	-.25
	Rt	.18	-.07	.21	-.01	.36	.23	.15	-.06
Hippocampus	Lt	.04	-.34	.39	-.08	.43*	.24	.24	.03
	Rt	-.05	-.31	.43*	-.09	.22	.07	.01	-.01

Note. N = 23; Lt, Left; Rt, Right; Sem, semantically-related; Pho, phonologically-related; Ort, orthographically-related; Re, rearranged; No, novel.

[a] bilateral frontal pole, left caudal middle frontal, bilateral rostral middle frontal, bilateral lateral orbital frontal, bilateral medial orbital frontal, right superior frontal, bilateral frontal pars orbitalis, bilateral frontal operculum.

* $p < .05$

Table 17

Correlation between Executive Function and Word Association Memory Performance on the MCI Group

	Item recognition		Immediate association				Delayed association			
	Immediate	Delayed	Hit	False alarm	*d'*	*β*	Hit	False alarm	*d'*	*β*
EF composite score	.36	.43	.28	-.29	.53*	-.06	.24	-.37	.49*	-.13

Note. N = 21.

* $p < .05$

Table 18

Performance on the Modified Recognition of Verbal Paired Associate Subtest of the WMS-III between Groups

	MCI (n = 21)	*HC (n = 24)*	*t*	*p*	Cohen's *d*
Original accuracy	90.48 (11.65)	97.74 (3.25)	-2.77	.011*	0.83
Modified accuracy	83.02 (13.60)	94.47 (4.71)	-3.67	.001**	1.10
Hit rate	80.95 (23.30)	95.83 (6.50)	-2.83	.010*	0.85
False alarm rate	17.78 (19.87)	6.00 (6.69)	2.59	.016*	0.77
Semantically-related	19.05 (22.40)	7.55 (9.21)	2.20	.037*	0.66
Rearrange	41.27 (32.75)	13.19 (20.84)	3.38	.002**	1.01
Novel	4.37 (20.00)	0.35 (1.70)	0.92	.370	-

Note. * $p < .05$; ** $p < .01$

Table 19

Relations between Associative Memory Measures and Brain Morphometry for All Participants

		Immediate				Delayed			
		Hit	FA	*d'*	*β*	Hit	FA	*d'*	*β*
Frontal lobe									
Frontal pole	Lt								
	Rt		*				*	*	
Caudal middle	Lt							*	
	Rt		*				*		
Rostral middle	Lt							*	
	Rt						*	*	
Lateral orbital	Lt				*				
	Rt							*	
Medial orbital	Lt								
	Rt								
Superior frontal	Lt							*	
	Rt		*				*		
Pars orbitalis	Lt								
	Rt								
Operculum	Lt								
	Rt						*	*	
Temporal lobe									
Parahippocampal	Lt								
	Rt								
Entorhinal	Lt	**		**				*	
	Rt	**		**	#	**		*	
Hippocampus	Lt		**	**			**	*	
	Rt			**				*	

Note. The asterisk represents significant correlation; the double signals in medial temporal lobes show significant relations even after controlling the frontal regions. The hashtag represents that the relation reached significant after controlling the frontal regions. The cingulate regions are not presented due to lack of correlations in those areas. FA, false alarm; Lt, left; Rt, right.

Table 20

Relations between False Alarm Type of the Word Association Task and Morphometric for All Participants

		Immediate association					Delayed association				
		Sem	Pho	Ort	Re	No	Sem	Pho	Ort	Re	No
Frontal											
Frontal pole	Lt										
	Rt	*		*				*	*		
Caudal middle	Lt										
	Rt	*		*			*			*	
Rostral middle	Lt	*									
	Rt	*					*				
Superior frontal	Lt			*			*				
	Rt	*		*			*				
Pars orbitalis	Lt										
	Rt										
Operculum	Lt	*					*				
	Rt	*					*		*	*	
Cingulate cortex											
Anterior	Lt										
	Rt										
Posterior	Lt								*		
	Rt								*		
Temporal											
Parahippocampal	Lt										
	Rt										
Entorhinal	Lt	*									
	Rt										
Hippocampus	Lt	*	**		**	**	* *	* *			* *
	Rt								*		#

Note. The asterisk represents significant correlation and the double signal in medial temporal lobe shows significance even after controlling the frontal regions. The hashtag represents that the relation reached significant after controlling the frontal regions. The medial and lateral orbital frontal regions are not presented due to lack of correlations in those areas. Lt, left; Rt, right; Sem, semantically-related; Pho, phonologically-related; Ort, orthographically-related; Re, rearranged; No, novel.

Figures

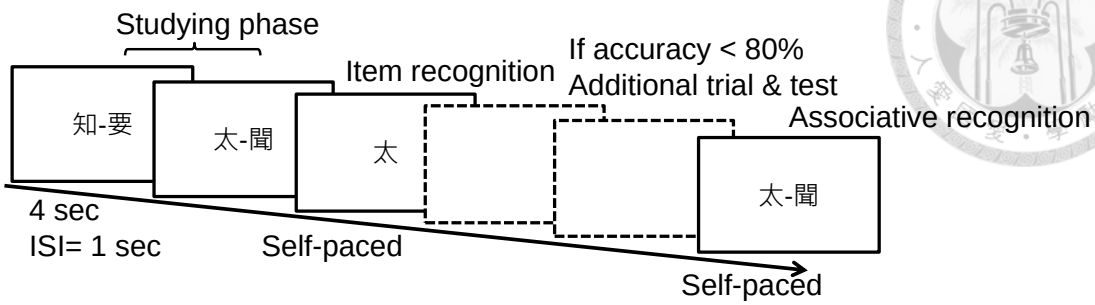

Figure 1. The paradigm of the word association task.

Note. ISI, inter-stimulus interval; sec, second.

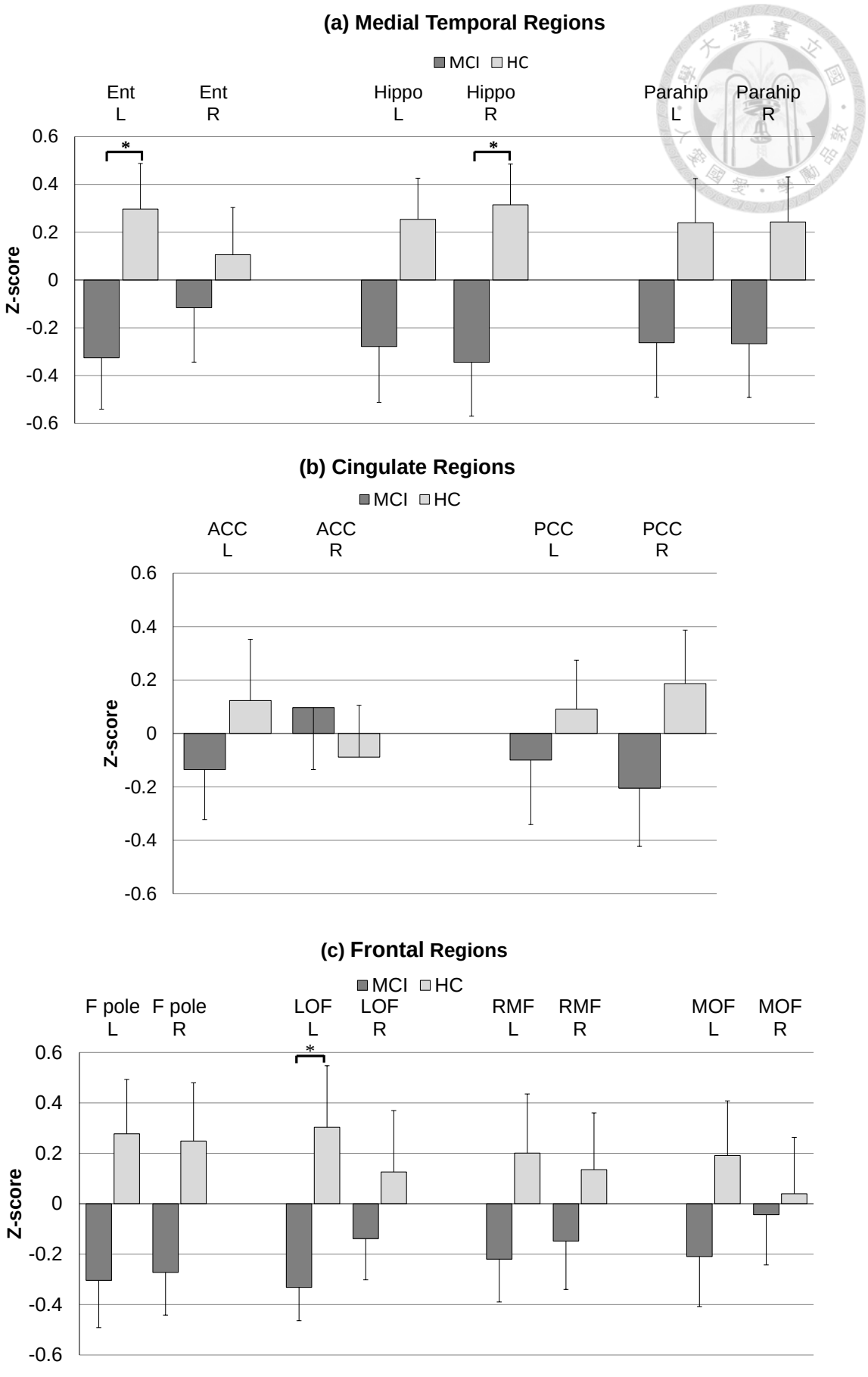
(a) Medial Temporal Regions
MCI HC
Ent L
Ent R
Hippo L
Hippo R
Parahip L
Parahip R
Z-score
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
*
*
(b) Cingulate Regions
MCI HC
ACC L
ACC R
PCC L
PCC R
Z-score
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
(c) Frontal Regions
MCI HC
F pole L
F pole R
LOF L
LOF R
RMF L
RMF R
MOF L
MOF R
Z-score
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
*

Figure 2. Bar chart shows brain morphometry for (a) medial temporal regions, (b) cingulate regions, and (c) frontal regions between groups. All values are standardized residuals (z-score) after regressing out the effect of gender. The hippocampus volumes are also regressed out the eTIV effect. Error bars shows standard error of the mean.

Note. L, left; R, right; Ent, entorhinal cortex; Hippo, hippocampus, Parahip, parahippocampal cortex; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; F pole, frontal pole; LOF, lateral orbital frontal cortex; RMF, rostral middle frontal cortex; MOF, medial orbital frontal cortex.

$^{*}p < .05$

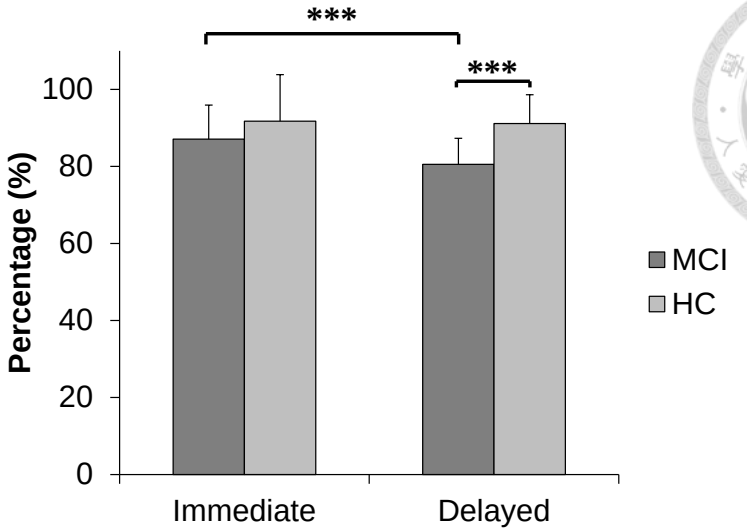

Figure 3. Bar chart shows the accuracy on the item recognition between groups. Error bars present standard deviation.

*** $p < .001$

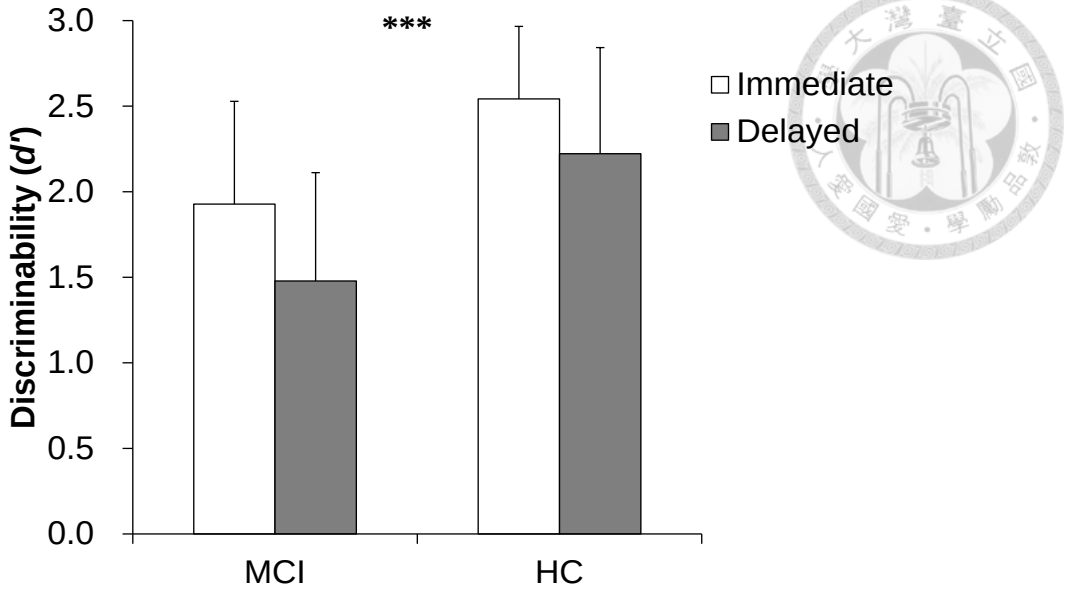

Figure 4. Bar chart shows the discriminability of the associative recognition between groups. Error bars present standard deviation.

*** $p < .001$

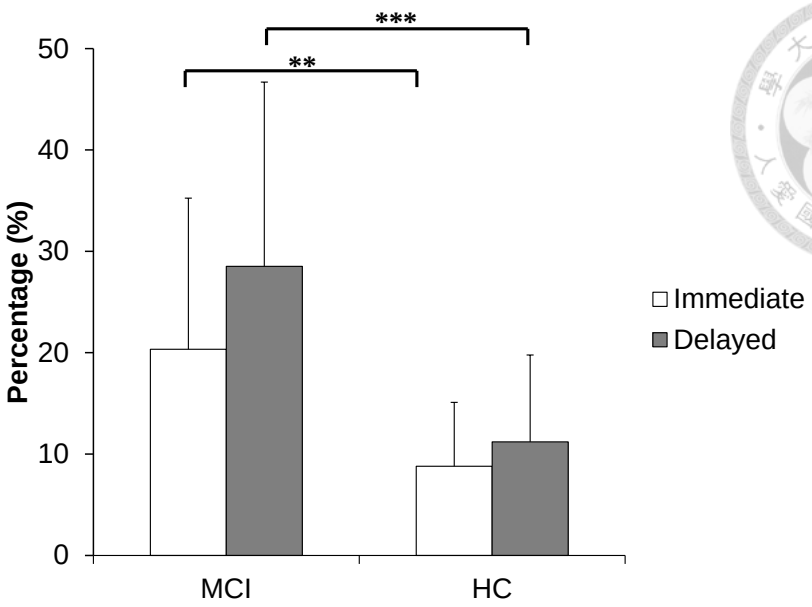

Figure 5. Bar chart shows the total false alarm rate on the associative recognition between groups. Error bars present standard deviation.
** $p < .01$; *** $p < .001$

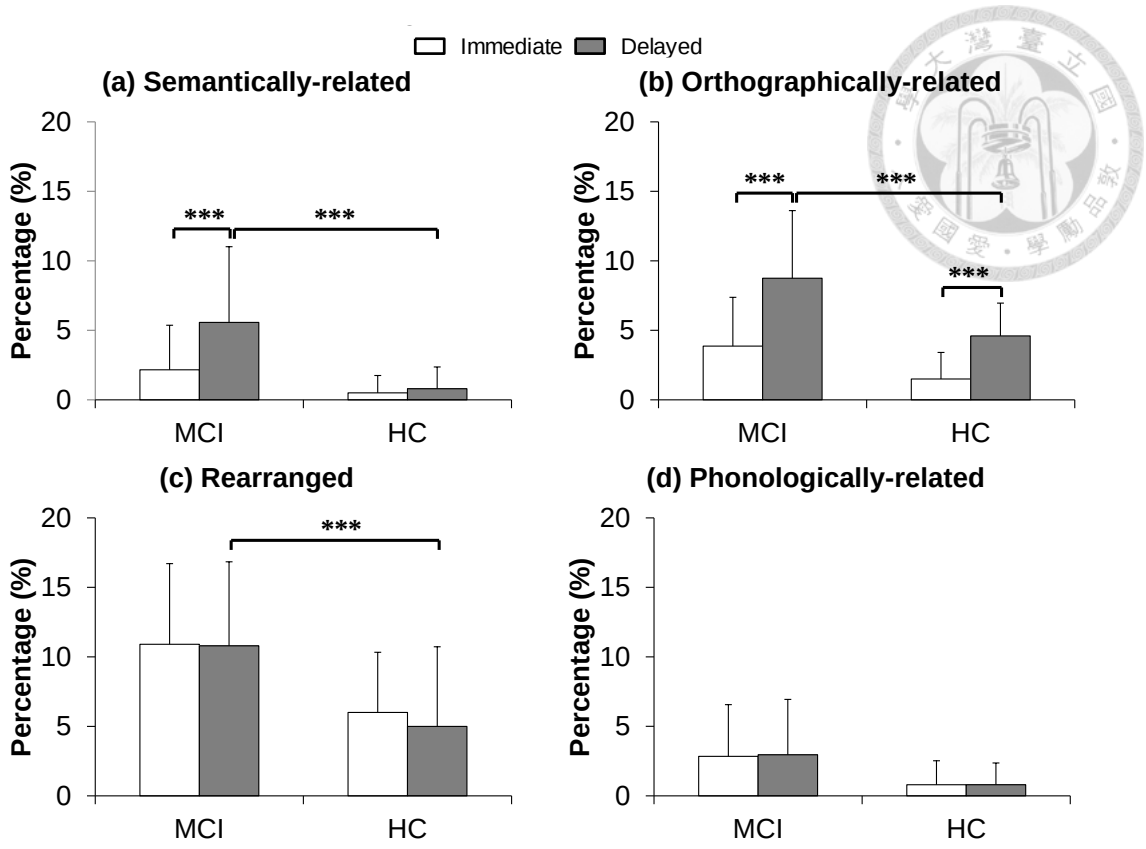

Figure 6. Bar charts present false alarm rate of (a) semantically-related, (b) orthographically-related, (c) rearranged, and (d) phonologically-related types on the immediate and delayed association between groups. Error bars show standard deviation.

* $p < .05$; *** $p < .001$

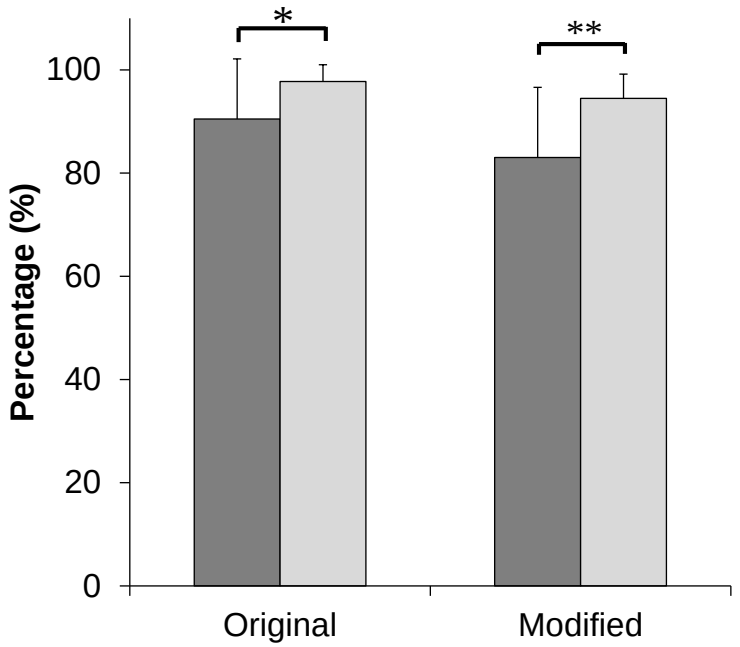

Figure 7. Bar charts present the accuracy of recognition of Verbal Paired Associate subtests of the WMS-III with the original and the modified versions between groups. Error bars show standard deviation.

* $p < .05$; ** $p < .01$