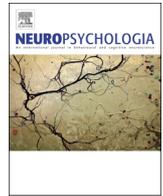




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# Associative memory and underlying brain correlates in older adults with mild cognitive impairment



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## ABSTRACT

This study investigated associative recognition memory by using unique features of the Chinese language and the underlying neuroanatomical correlates. The study participants were 22 Chinese speakers with mild cognitive impairment (MCI) and 25 cognitively normal (CN) Chinese speakers. The results revealed that the MCI group demonstrated impaired associative memory performance, despite exhibiting item memory performance comparable with that of the CN group, and that associative memory performance in older adults was associated with gray matter integrity in the medial temporal regions as well as executive function. An abnormal elevation was also observed in false-positive errors related to features unique to Chinese characters, namely orthographical errors, in addition to rearranged and semantic errors in the MCI group relative to the CN group, and the three error subtypes were differentially associated with gray matter integrity in the hippocampus or lateral prefrontal regions. Overall, these results demonstrate the value of evaluating associative memory in people with prodromal Alzheimer's disease (AD), and further elucidate the underlying neural substrates related to associative recognition memory in older adults.

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## 1. Introduction

Mild cognitive impairment (MCI), characterized by hippocampal atrophy relative to healthy aging, is well established as a risk state for the development of dementia (Petersen et al., 2001). Evidence from previous neuropsychological studies has suggested that people with MCI have difficulty in tests involving list learning (e.g., word lists) (Chang et al., 2010a; Chen et al., 2011; Libon et al., 2011; Moser et al., 2014) as well as tests that measure associative memory (e.g., word–word or object–location pairs) (Fowler et al., 2002; Lowndes and Savage, 2007; Pike et al., 2012), which refers to the binding of multiple pieces of information into a single memory trace (Cohen et al., 1997).

The abilities to detect novel items (Tulving et al., 1994) and establish associations between components of memory episodes (Cohen et al., 1997) have been indicated as crucial functions of the hippocampus. However, lesion studies have found disproportionate associative memory impairment relative to item memory impairment in patients with selective hippocampal lesions (Kroll et al., 1996; Mayes et al., 2004; Vargha-Khadem et al., 1997). This is

particularly prevalent when tests employ a recognition format in which the item memory recognition, but not associative memory recognition, can still be performed through the familiarity process. In MCI, however, the question concerning whether impairment in associative memory is disproportionate to deficits in memory for individual items remains underinvestigated. Although a few studies (Hanseeuw et al., 2011; Troyer et al., 2012, 2008) that have addressed this question have demonstrated that people with MCI have poorer associative memory relative to item memory, methodological concerns have raised questions regarding the interpretation of their results. For example, because retrieving associations is often more difficult than retrieving single items (Chalfonte and Johnson, 1996; Mayes et al., 2004; Naveh-Benjamin et al., 2003; Turriziani et al., 2004; Vargha-Khadem et al., 1997; Wang et al., 2013), people with poor memory, such as older adults with MCI, may exhibit associative memory impairment simply because of increasing task difficulty, rather than because of differential impairment in associative memory capacity (Kroll et al., 1996). In other words, the poor associative memory in MCI relative to cognitively normal (CN) older adults might result from a floor effect on item memory in MCI, rather than disproportionate impairment in the associative memory compared with item memory. Most previous studies have examined the problem at the statistical rather than research design level by including item memory as a covariate in analysis (Hanseeuw et al., 2011; Troyer et al., 2012,

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2008). To overcome the methodological confounders reported in the literature, the current study investigated the verbal associative memory performance of people with MCI by equating item memory performance during the encoding phase, prior to assessing the associative memory performance.

Lesion and functional imaging studies have suggested that episodic memory draws on a widespread network of brain structures including the hippocampal formation and frontal lobe (Buckner, 1996; Cabeza and Nyberg, 2000). Structural imaging studies have reported a significant relationship between memory performance and gray matter volume of the lateral prefrontal regions in healthy older adults (Van Petten et al., 2004) and people with MCI (Chang et al., 2010b). The susceptibility of episodic memory to MCI may thus reflect that performance could be disrupted because of changes at multiple sites in a large distributed network. Although the link between medial temporal atrophy and memory decline is well established in MCI, the impact of the integrity of brain regions in the frontal lobes on memory function, particularly regarding that of the lateral prefrontal regions on the associative memory, is less understood.

Whereas research concerning verbal associative memory in people with Alzheimer's disease (AD) or MCI has focused on English speakers (Giovanello et al., 2004; Lowndes et al., 2008), few studies have investigated Chinese speakers. Chinese contrasts with English in both the spatial layout of visual forms and the mapping of these forms to meaning and pronunciation. At the script level, Chinese character forms are complex visual-spatial configurations. At the mapping level, each character maps to a single-syllable morpheme, thus allowing a direct connection from orthography to meaning, as well from orthography to syllable-level phonology. A unique feature of the Chinese language is that there are numerous homophones among Chinese characters. For example, for the 4000–5000 syllables encountered in daily Chinese language use, the number of possible written syllabic forms is only approximately 400 (Chen and Juola, 1982). Prior studies have suggested that perceptually similar features interfere with the visual discrimination and working memory performance of CN older adults and people with MCI (Ally et al., 2013; Chen, 2007; Lin et al., 2015; Newsome et al., 2012). Furthermore, phonological similarity has been reported to affect the performance in working memory and item memory of Chinese-speaking adults (Lai, 2008; Lin et al., 2015). However, it remains unknown whether the unique features of Chinese characters affect associative memory in people with MCI. Hence, the present study also explored whether the phonological and orthographic features of Chinese characters could affect associative memory in Chinese speakers with MCI relative to CN Chinese-speaking older adults. We expected that compared with CN older adults, people with MCI would be more prone to make errors regarding stimuli that shared similar phonological and orthographic features with the target stimuli.

Accordingly, the present study investigated the performance in item versus associative memory of people with MCI relative to CN older adults, and to elucidate the neural correlates of associative memory. We hypothesized that people with MCI would exhibit disproportionate impairment in associative memory compared with item memory, relative to CN older adults. We further hypothesized that, consistent with previous studies in MCI (e.g., Chang et al., 2010a; Troyer et al., 2012), gray matter changes in medial temporal lobe structures – particularly the hippocampus – would be pronounced in MCI compared with CN older adults. Furthermore, the associative memory performance would be associated with brain integrity in the hippocampus and medial temporal lobe structures, and to a lesser extent, the lateral prefrontal lobe regions.

## 2. Materials and methods

### 2.1. Participants

The study sample comprised 22 older adults with MCI and 25 age- and education-matched cognitively normal older adults (CN) recruited from National Taiwan University Hospital, Taipei City Hospital, and nearby residential communities. Participants were excluded if they had current or past diagnoses of neurological or psychiatric disorders, alcohol or drug abuse, learning disabilities, known head injury involving a loss of consciousness, untreated hypothyroidism, or any severe visual or auditory impairment precluding participation in neuropsychological testing. The present study was part of an ongoing aging study, and was approved by the ethics committees and institutional review boards of both National Taiwan University Hospital and Taipei City Hospital. Written informed consent was obtained from all the participants. Table 1 presents the demographic and clinical characteristics of the participants.

A participant was classified as having MCI on the basis of three criteria recommended by the International Working Group (Winblad et al., 2004): (1) neither normally aging nor having dementia, (2) having generally preserved functional activities, and (3) showing evidence of cognitive decline by a subjective evaluation and/or an informant report with objective data. Objective cognitive impairment was determined according to criteria suggested by Jak and colleagues (Jak et al., 2009), requiring scores on at least two measures (within at least one cognitive domain) that are one standard deviation or more below age-appropriate norms. A comprehensive list of neuropsychological measures used for the group classification is presented in Table 2 (excluding FSIQ-estimated measures). According to the aforementioned criteria, the MCI group comprised 19 participants classified as having amnesic MCI (11 single-domain, eight multiple-domain), and three classified as having nonamnesic MCI (all single-domain in the executive function). The Clinical Dementia Rating Scale (CDR) (Hughes et al., 1982) was administered to all the participants and their caregivers; all CN older adults had a global CDR score of 0, and all the participants with MCI had a score of 0.5.

### 2.2. Neuropsychological evaluation

All the participants underwent a neuropsychological battery test assessing cognitive functioning in five domains: attention, language, visuomotor and visuospatial, learning and memory, and executive function. The following tests were used to assess the five neuropsychological domains: (1) attention: standardized Taiwanese versions of the Digit Span Forward length of the Wechsler Adult Intelligence Scale, Third Edition (WAIS-3) (Chen and Chen, 2002) and Spatial Span Forward length of the Wechsler Memory Scale-III (WMS-3) (Hua et al., 2005); (2) language: the WAIS-3 Vocabulary subtest, Category Fluency (animal) and 30-item Boston Naming Test (Kaplan et al., 1983); (3) visuomotor and visuospatial: the Color Trails Test Part 1 (D'Elia et al., 1996) and Digit Symbol Substitution and Block Design subtests of the WAIS-3; (4) learning and memory: the Logical Memory (LM) and Visual Reproduction (VR) subtests of the WMS-3; and (5) executive function: a modified Wisconsin Card Sorting Test (Nelson, 1976), the Design Fluency Test (switching condition) of the Delis–Kaplan Executive Function System (D-KEFS) (Delis et al., 2001), the Stroop task (interference condition) (Golden, 1978), and Color Trails Test Part 2 (D'Elia et al., 1996). To eliminate the confounding effect of motor processing speed, the time difference between Parts 1 and 2 was used as an indicator of executive function. An estimated full-scale intelligence quotient was obtained using a linear equating model based on four subtests of the standardized Taiwanese version of the WAIS-3 (i.e., Similarities, Matrix Reasoning, Arithmetic, and Digit Symbol Substitutions), which was proven to be valid with favorable time efficiency (Chen et al., 2008). In addition to completing cognitive measures, all the participants completed the Geriatric Depression Scale (GDS) (Burke et al., 1991).

**Table 1**

Demographic and clinical characteristics of the mild cognitive impairment (MCI) and cognitively normal (CN) groups.

	MCI	CN	<i>p</i> Value
	<i>n</i> =22 (mean S.D.)	<i>n</i> =25 (mean S.D.)	
Age	73.77 (7.70)	70.68 (5.45)	0.125
Education	12.50 (2.92)	13.68 (2.87)	0.170
Gender (women/men)	12/10	15/10	0.706
Geriatric Depression Scale	3.55 (3.74)	3.28 (2.96)	0.787
FSRP % stroke risk	15.18 (9.79)	11.92 (9.72)	0.258
CDR-SB	1.27 (1.22)	0.59 (0.49)	0.021*

Note: FSRP, Framingham Stroke Risk Profile; CDR-SB, Clinical Dementia Rating Scale-Sum of Boxes.

\*  $p < 0.05$ .

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