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RESEARCH ARTICLE

Working Memory Precision and Associative Binding in Mild Cognitive Impairment

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ABSTRACT

To better understand working memory (WM) deficits in Mild Cognitive Impairment (MCI), we examined information precision and associative binding in WM in 21 participants with MCI, compared to 16 healthy controls, using an item-location delayed reproduction task. WM, along with other executive functions (i.e. Trail Making Task (TMT) and Stroop task), were measured before and after a 2-h nap. The napping manipulation was intended as an exploratory element to this study exploring potential impacts of napping on executive functions.

Compared to healthy participants, participants with MCI exhibited inferior performance not only in identifying encoded WM items but also on item-location associative binding and location precision even when only one item was involved. We also found changes on TMT and Stroop tasks in MCI, reflecting inferior attention and inhibitory control. Post-napping performance improved in most of these WM and other executive measures, both in MCI and their healthy peers.

Our study shows that associative binding and WM precision can reliably differentiate MCIs from their healthy peers. Additionally, most measures showed no differential effect of group pre- and post-napping. These findings may contribute to better understanding cognitive deficits in MCI therefore improving the diagnosis of MCI.

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Introduction

Memory impairments are central to clinical diagnosis of Alzheimer Disease (AD) and Mild Cognitive Impairment (MCI; Kessels, Feijen, & Postma, 2005). Although deficits in long-term episodic memory have been well documented, research has shifted to working memory (WM) dysfunction. While earlier studies of WM in participants with AD/MCI focused on the central executive component or slot-like capacity of WM (Gagnon & Belleville, 2011; Huntley & Howard, 2010; Kirova, Bays, & Lagalwar, 2015; Saunders & Summers, 2011), recently the focus changed to information registration processes of WM,

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such as memory duration, information precision, or associative binding (Liang et al., 2016; Lu, Neuse, Madigan, & Dosher, 2005).

Improved Measurement of WM in AD/MCI

Information registration processes in AD/MCI have been measured through the number of items that were correctly remembered in change detection delay-match-to-sample, or visual short-term memory (VSTM) paradigms (Parra et al., 2009, 2010, 2011). However, a recall or recognition failure does not necessarily mean that an item is completely forgotten. Further, the precision of the information may vary even if items are correctly retrieved (Bays & Husain, 2008; Pertzov et al., 2013). More recent work proposed a paradigm of capturing both information precision and associative binding (i.e., misbinding information from different sources) in WM (for a review see Ma, Husain, & Bays, 2014). For example, in the Oxford "What was where?" task (referred to as the Oxford Memory Task (OMT)) hereafter, Bays and Husain (2008), participants are presented with different numbers of visual stimuli (i.e., fractal objects) in different trials followed by a blank-screen delay. They are then asked to recognize the encoded fractal object from lures and drag the identified target to the exact location on the screen where it is originally located. The advantage of the task is that in addition to measuring the accuracy of identifying the encoded items, the precision of the spatial information in WM can be obtained by measuring the distance between the retrieved and original location of the target item (Zokaei & Husain, 2019). Furthermore, when more than one item is involved in a trial, associative binding processing can be probed by examining whether one item is placed at the location that belongs to the target or another unprobed item (Liang et al., 2016).

Deficits in WM in AD and MCI

Using OMT or similar tasks, studies reported that participants with AD or MCI were impaired not only in memory precision but also showed specific impairments in binding the item-location information (Liang et al., 2016; Pertzov, Dong, Peich, Husain, & Howe, 2012), resembling the memory deficits in temporal lobe lesion patients (Hannula, Tranel, & Cohen, 2006; Libby, Hannula, & Ranganath, 2014, 2014; Watson, Voss, Warren, Tranel, & Cohen, 2013). Thus, such impairments in associative binding in participants with AD/MCI or older adults (compared to young adults) may be linked to the hippocampus or adjacent medial temporal lobe (MTL) structures that might be essential for associative binding (Burgess, Maguire, & O'keefe, 2002; Kessels, de Haan, Kappelle, & Postma, 2001; Pertzov et al., 2013). Using the OMT, previous studies also found that even family members of familial Alzheimer disease (FAD) patients who are asymptomatic performed worse on the associative binding component of the task (Liang et al., 2016; Pavisic et al., 2021). This is important because previous studies have focused on only AD patients rather than individuals with memory impairment. As one of the first studies to examine different measures of WM, the current study contributes to better identifying MCI or older adults in general who may be at risk of developing AD (Aurtenetxe et al., 2016; Kirova, Bays, & Lagalwar, 2015).

Goal of the Study

The current study aims to compare participants with and without MCI on memory precision and associative binding in WM on the OMT task. We hypothesized that compared to healthy controls, participants with MCI would show inferior WM performance, especially on the item-location memory binding and location precision measures as well as those trials with higher load and longer delay. To examine how other aspects of executive functions, such as attention and inhibitory control, can be affected similarly in MCI, we also included the Trail Making Task (TMT) and Stroop Color-Word Test, in which participants with MCI have also showed impairments in prior studies (Bastug et al., 2013; Campbell, Murphy, & Stauble, 2005; Chen et al., 2013). We hypothesized that participants with MCI would have worse performance (i.e. lower accuracy or/and slower reaction time) in TMT and Stroop tasks when compared to the healthy controls. In addition, napping has recently been implicated to have equivalent restorative function like sleep (Cross et al., 2015), which might be a consequence of removing potential neurotoxic waste products like β-amyloid (Aβ), α-synuclein, and *tau*. These waste products have been linked to neurodegenerative disease like AD and MCI (Holth et al., 2019; Ju et al., 2017; Lucey et al., 2019; Xie et al., 2013). However, previous research reporting post-nap cognitive improvements mostly implemented conventional recall tasks and focused on WM capacity (Nguyen, Tucker, Stickgold, & Wamsley, 2013; Schneider et al., 2015). It remains unclear how WM precision and associative binding may differentially affect older adults with and without MCI. In our design, as we implemented a unique WM task, we would like to take this opportunity to explore the potential beneficial effects of napping on the novel perspectives of WM. Thus, we administered the tasks before and after napping for both groups. Given that we did not feature a non-napping control group, we considered this as an exploratory question. The ultimate aim is to contribute to a growing body of literature on better understanding cognitive deficits in MCI that might help to design improved diagnosis of early cognitive impairment.

Methods

Participants

Twenty-one participants with MCI and 16 healthy controls were recruited from College Station – Texas through the subject database in the Center for Translational Research in Texas A&M University as well as mass e-mails sent by university listservs. Inclusion criteria for both groups were (1) physically healthy male or female aged over 5 years old; (2) fluent English speaker; (3) ability to walk, sit down and stand up independently; and (4) without any clinically diagnosed sleep disorders. We also obtained medication use information from all participants. In the healthy group, 69% of them reported not taking any medicine and 31% were taking 2 or more than 2 medicines. While for the MCI group, 19% reported not taking any medicine, 14% reported taking 1 medicine, and 67% taking 2 or more medicines. Since the effects of multiple medicines on cognition were not clear and not the focus of the study, we did not include the data in the current analyses. Written informed consent was obtained from all participants before performing any study-related procedures. The study was approved by the Institutional Review Boards at Texas A&M University. Participants received $100 compensation at the end of study.

Participants were categorized into either MCI or Healthy group based on the Montreal Cognitive Assessment (MoCA) scores, which detects MCI and early AD. It assesses different cognitive domains including attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation (Nasreddine et al., 2005). The MCI group included participants with a MoCA score between 19 and 26, and the Healthy group included participants with a MoCA score equal to or greater than 26 (Nasreddine et al., 2005). All participants with MCI were able to track the appointment schedules, follow the research instructions, complete tasks independently, and successfully carry out daily social interactions, suggesting that they did not have severe mental or physical impairment and less likely had dementia.

Procedure

Participants were assessed at the Center for Translational Research at Texas A&M University. The study design included 2 sessions. The first one was a screening visit, in which participants completed demographic information and cognitive assessments to confirm their eligibility of participation. Body weight, height, and vital signs were measured as well. On average, participants completed the screening session within 2 h. During the screening session, participants were also given the opportunity to familiarize with the study set up (e.g., the neurobiological napping measure sensors). Research staff then invited the eligible participants for the following study procedure. The second session was the study visit, in which participants completed all the cognitive tasks in a fixed sequence (Stroop, TMT, WM task), before and after a two-hour nap. On average, participants finished three tasks within 5 min.

Measures

Oxford 'What Was where?' Short-Term Memory Task

The Oxford Memory Task (OMT) is a spatial working memory and item-location binding task specifically designed for participants with cognitive impairment (Pertzov et al., 2013). It contained 2 practice blocks with 10 trials for each and followed by 3 test blocks with 40 trials for each. In each trial, either 1 or 3 fractal objects randomly located on the screen for 1 or 3 s, respectively. Participants were instructed to remember both the fractals and the locations. A blank delay screen was then displayed randomly for 1 or 4 s, followed by a test array with two vertically presented fractals, in which one was the target and the other was a foil. Participants were directed to pick the target fractal and drag it to the remembered location. A schematic representation of the task is shown in Figure 1.

OMT performance was measured by the proportion of correct responses, absolute errors, misbinding errors, errors due to guessing, identification times, and localization times. Specifically, the proportion of correct responses was measured by the proportions of trials in which the targets were correctly chosen. The absolute error, calculated as the distance between response and the true location, was used to reflect the spatial memory precision. Then each response was categorized depending on which of the following distances was the shortest: the distance between the response location to (D1) the target location, (D2) the location of the closest non-target, i.e., the closest item that is not being probed, and (D3) the location of another randomly chosen trial's non-target. The response was counted as

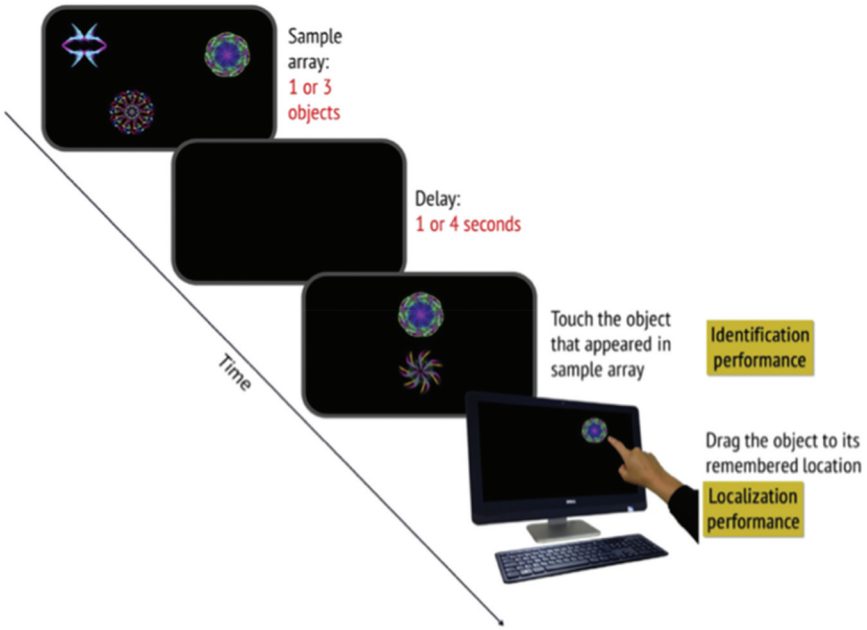

Figure 1. Schema of Oxford "what was where?" memory task (OMT) (Pertzov et al., 2013). one or three fractals were presented in different locations. after a 1- or 4-second delay, a target and a foil fractal were presented. participants were required to identify the target (two alternative forced choices) and move it to its original location.

"target," "misbinding," or "random/guessing" if D1, D2, or D3 was the shortest, respectively. Misbinding errors occurred when participants picked the correct fractal but placed it in the location of one of the other items. Error due to guessing accounted for the responses that are completely a result of random guessing, i.e., placing the target at a location that is not close to the current trial's target and non-target location. The proportion of misbinding error and error due to guessing were quantified by the proportion of times a response was "misbinding" or "random/guessing" (for more details on the task, please see, Grogan et al., 2020; Pertzov et al., 2013). Identification time was measured by the reaction time during which participants picked the object from the test array. Localization time was measured by the reaction time during which participants dragged and placed the object.

Trail Making Test (TMT)

The Trail Making Test (TMT) is a neuropsychological test assessing visual attention and task switching (Arnett & Labovitz, 1995) which provides information about visual search speed, scanning, speed of processing, mental flexibility, as well as executive functioning. The test was performed in SmartStrokes testing suite (Lara-Garduno, Leslie, & Hammond, 2016) on a Windows Surface book with a Surface pen. It consisted of two parts in which participants were instructed to connect a sequence of 25 targets as quickly as possible while still maintaining the accuracy. In part A, targets were all numbers (e.g. 1, 2, 3, etc.), while in part B, targets were altered between numbers and letters (e.g. 1, A, 2, B, etc.). If participants made an error, the test administrator corrected them before they moved to the next target.

Participants' performance was measured by both error rate and reaction time. Previous studies showed that the Cronbach's alpha for part A ranged from 0.76 to 0.89, and from 0.86 to 0.94 for part B, indicating good to excellent reliability of TMT (Poreh, Miller, Dines, & Levin, 2012; Wagner, Helmreich, Dahmen, Lieb, & Tadić, 2011).

Stroop Color-Word Task

The Stroop task assesses shifting attention and the decline abilities for competing processes (Stroop, 1992). The stimuli were shown on a white sheet of paper that was landscape oriented. It consisted of two conditions. For the congruent condition, the displayed color words were printed in a congruent color, for example, the word yellow printed in yellow ink. For the incongruent condition, color words were printed in incongruent color, for example, the word yellow printed in red ink. Participants were instructed to name the ink color of the printed words as quickly and accurately as possible. Participants' performance was measured by both error rate and reaction time. Previous studies showed that the Cronbach's alpha ranged from 0.70 to 0.96 indicating good to excellent reliability of Stroop Color-Word Task (Ataya et al., 2012; DiBonaventura, Erblich, Sloan, & Bovbjerg, 2010).

Analysis Plan

For demographic variables, *t*-test and Chi-square test were conducted to test differences of continuous and categorical variables separately. Analysis of Covariance (ANCOVA) was performed on the different measures from three tasks separately. For the OMT, Item (1item or 3item), Delay (1sec or 4sec), Session (Time1 or Time2, i.e., pre-nap or post-nap) and Group (MCI or Healthy) were included as independent variables. We explored how these factors impact proportion for correct response, absolute error, misbinding error, error due to guessing, identification time, and localization time. For TMT, we investigated how Condition (number-only or number-letter), Session (Time1 or Time2), and Group (MCI or Healthy) affected error rate and reaction time. For the Stroop task, we examined how Session (Time1 or Time2) and Group (MCI or Healthy) impacted error rate and reaction time. For all statistical testing, age and sex were entered as covariates. To eliminate effects of potential outliers, winsorizing procedure was used to set extreme values below 5th percentile or above 95th percentile to be at 5th and 95th percentile, respectively (https://www.mathworks.com/matlabcentral/fileexchange/32327-winsorising-data). This procedure was applied for individual conditions in each group to ensure statistical analyses would not be affected by any potential outliers. The statistical significance level is set at $p < .05$. All analyses were conducted in R (R Core Team, 2013).

Table 1. Demographic information for group.

Variables		Healthy ($n = 16$)	MCI ($n = 21$)	*p*-value
Demographics				
	Age	68.18	74.00	.016
	Gender (Female/Total)	11/16	9/21	.141
	BMI	27.64	27.06	.832
Cognition				
	MoCA	26.88	22.62	<.001

Note: MCI = Mild Cognitive Impairment; BMI = Body Mass Index; MoCA = Montreal Cognitive Assessment.

Results

Demographic Information

Table 1 shows the demographic for the participants broken down by Group to characterize our sample. As expected, the MoCA scores for participants with MCI were significantly lower than the healthy controls ($t(35) = -7.44$, $p < .001$). Participants with MCI were significantly older than the healthy controls ($t(35) = 2.53$, $p = .016$). No group differences were found on sex ($x^2(1) = 1.52$, $p = .141$) or Body Mass Index (BMI, $t(35) = 0.21$, $p = .832$).

To further confirm that participants with MCI had memory deficits compared to healthy controls, we extracted their performance on the MoCA memory subscale. We conducted an ANCOVA with age as a covariate and found participants with MCI performed significantly worse on this memory scale, $F(1,34) = 24.40$, $p < .001$, $\eta^2 = .418$. Additional data supporting our classification of MCI and healthy controls can be found in Appendix I.

Cognitive Performance

Oxford 'What Was where?' Memory Task (OMT)

For the memory task, ANCOVA was run to investigate the impact of Group (MCI, Healthy), Item (1-item, 3-item), Delay (1-sec, 4-sec), and Session (Time1, Time2) on task performance (i.e., proportion for correct response, absolute error, error due to guessing, identification time, localization time). Since misbinding error can be calculated only for the 3-item condition, only Group, Delay, and Session were included in the ANCOVA. Age and sex were entered as covariates. All results remained the same after outliers were winsorized. For an overview of ANCOVA results, please see Table 2.

The results for proportion of correct recognition revealed significant main effects of Group ($F(1,29) = 10.38$, $p = .003$, $\eta^2 = .264$), Item ($F(1,29) = 4.61$, $p = .040$, $\eta^2 = .137$), Delay ($F(1,29) = 49.59$, $p < .001$, $\eta^2 = .631$), and Session ($F(1,29) = 4.81$, $p = .036$, $\eta^2 = .142$). Post hoc comparisons using Tukey HSD revealed that (1) healthy controls had a significantly higher proportion of correct response than participants with MCI ($t(33) = 2.94$, $p = .003$); (2) both groups had a significantly higher proportion of correct response for 1-item condition than 3-item condition ($t(33) = 1.81$, $p = .040$); (3) both groups had significantly higher proportion of correct response for 1-sec delay than 4-sec delay ($t(33) = 7.04$, $p < .001$); and (4) both groups had a significantly higher proportion of correct response for Time2 than Time1 (t

Table 2. ANCOVA results of Oxford memory task.

	Group effect MCI vs. Healthy		Session effect Time1 vs. Time2		Item effect 1item vs. 3item		Delay effect 1sec vs. 4sec	
Measure	$F(1,29)$	η^2	$F(1,29)$	η^2	$F(1,29)$	η^2	$F(1,29)$	η^2
Proportion of correct response	10.38**	0.26	4.81*	0.14	4.61*	0.14	49.59***	0.63
Absolute error	7.49*	0.21	10.86**	0.27	222.56***	0.89	8.48**	0.23
Misbinding error rate	8.27**	0.22	7.77**	0.21	-	-	4.20*	0.13
Error due to guessing	7.58*	0.21	5.48*	0.16	23.07***	0.44	19.45***	0.40
Identification time	1.84	-	9.10**	0.24	45.47***	0.61	25.28***	0.47
Localization time	3.29	-	10.63**	0.27	46.76***	0.62	20.94***	0.42

Note: *$p<.05$, **$p<.01$, ***$p<.001$. The table only summarizes the main effects of the ANCOVAs. For interaction effects, only the proportion of correct response showed significant Group by Item and Session by Item interactions (for detailed statistics, see the main text).

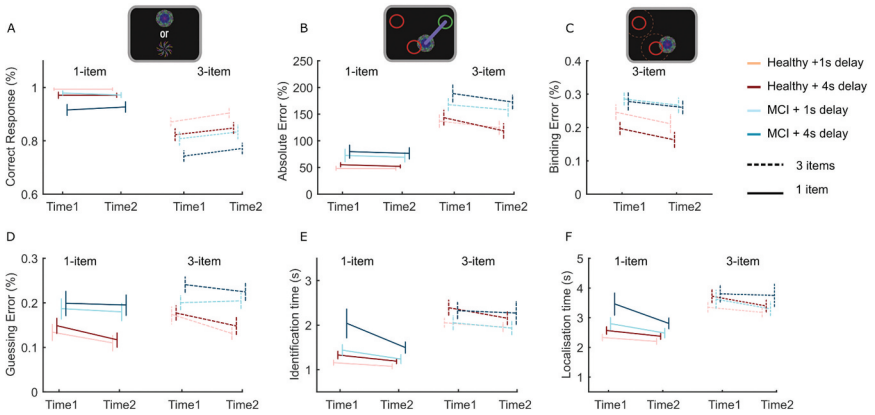

Figure 2. Mean performance on different Oxford memory test (OMT) measures. performance with one (in regular line) and three (in dotted line) items for healthy controls with 1-sec delay (orange), healthy controls with 4-sec delay (red), participants with MCI with 1-sec delay (light blue), and participants with MCI with 4-sec delay (dark blue). (A) proportion of correct response. (B) absolute error. The image above shows an example relevant to the calculation. circles represent the original locations of the target fractal (green) and two others (red); blue lines illustrate the localization errors used in the above plots. (C) misbinding error. (D) guessing error. (E) identification time. (F) localization time. Note: error bars represent ± standard error. time1: pre-napping; time2: post-napping. The illustrations above A, B, and C are from (Pertzov et al., 2013) with permissions.

Table 3. Descriptive statistics of task performance by group & time.

	Healthy (n = 16)		MCI (n = 21)	
	T1	T2	T1	T2
Variables	mean (*SD*)	mean (*SD*)	mean (*SD*)	mean (*SD*)
Oxford Memory Task				
Proportion of correct response	0.91(0.09)	0.93(0.08)	0.87(0.12)	0.88(0.11)
Absolute error	96.76(14.45)	86.56(12.83)	119.81(16.96)	115.49(14.93)
Misbinding error rate	0.11(0.03)	0.09(0.03)	0.14(0.03)	0.13(0.03)
Error due to guessing	0.16(0.02)	0.13(0.02)	0.21(0.02)	0.20(0.02)
Identification time	1.73(0.17)	1.60(0.15)	1.87(0.22)	1.69(0.19)
Localization time	3.00(0.21)	2.79(0.19)	3.28(0.30)	3.05(0.27)
Trail Making Task				
Error rate	0.03(0.01)	0.02(0.01)	0.04(0.01)	0.02(0.01)
Reaction time	58.28(7.27)	30.94(3.00)	96.21(13.25)	41.64(4.20)
Stroop Task				
Error rate	0.01(0.02)	0.02(0.02)	0.03(0.02)	0.03(0.02)
Reaction time	96.44(23.57)	91.47(21.09)	115.68(37.55)	112.65(20.59)

Note: T1 = Time1/pre-napping; T2 = Time2/post-napping.

(33) = 1.86, p = .036). However, the Session by Group interaction effects were not significant (F(1,29) = .001, p = .982, see Figure 2A and the marginal means in Table 3).

The results also showed a significant interaction effect between Group and Item (F(1,29) = 5.20, p = .030, η^2= .152). Post hoc analysis using Tukey HSD indicated that healthy controls showed significantly higher proportion of correct response than participants with MCI in the 3-item condition (t(33) = 2.89, p = .003), but no significant differences in the 1-item condition (t(33) = 0.40, p = .654), indicating that participants with MCI showed impairment only when the task difficulty level was high. The results also revealed

a significant interaction effect between Session and Item ($F(1,29) = 5.13$, $p = .031$, $\eta^2 = .150$). Post hoc analysis using Tukey HSD indicated that participants showed significantly higher proportion of correct response in Time2 than Time1 in the 3-item condition ($t(33) = 3.23$, $p = .001$), but no significant differences in the 1-item condition ($t(33) = 1.36$, $p = .090$), which may be due to the ceiling effect of 1-item performance. All other interaction effects among the four factors were not significant (all ps > .05). Older participants showed worse performance than younger participants ($F(1,29) = 9.56$, $p = .004$, $\eta^2 = .248$).

The results for absolute error (i.e. absolute distance from the response location to the targeted fractal) showed significant main effects of Group ($F(1,29) = 7.49$, $p = .011$, $\eta^2 = .205$), Item ($F(1,29) = 225.56$, $p < .001$, $\eta^2 = .886$), Delay ($F(1,29) = 8.48$, $p = .007$, $\eta^2 = .226$), and Session ($F(1,29) = 10.86$, $p = .003$, $\eta^2 = .272$). Post hoc comparisons using Tukey HSD indicated that participants with MCI had significantly more absolute error than the healthy controls when the two difficulty levels were combined ($t(33) = 2.40$, $p = .011$) or separated ($p = .021$ for 1-item and .01 for 3-item), indicating that MCI participants' memory for item locations was less precise compared to healthy controls even when encoding one single item. The results also showed (1) both groups had significantly more absolute error for 3-item condition than 1-item condition ($t(33) = 15.02$, $p < .001$); (2) both groups had significantly more absolute error for 4-sec delay than 1-sec delay ($t(33) = 2.60$, $p = .007$); and (3) both groups had significantly more absolute error in Time1 than Time2 ($t(33) = 2.94$, $p = .003$). However, Session by Group interaction effects were not significant ($F(1,29) = 0.96$, $p = .334$, see Figure 2B and the marginal means in Table 3). The results revealed no other significant interactions among the four factors (all ps > .05). Participants with older age also showed higher absolute errors than those with younger age ($F(1,29) = 4.74$, $p = .038$, $\eta^2 = .140$).

The results for misbinding error revealed significant main effects of Group ($F(1,29) = 8.27$, $p = .007$, $\eta^2 = .222$), Delay ($F(1,29) = 4.20$, $p = .050$, $\eta^2 = .127$), and Session ($F(1,29) = 7.77$, $p = .009$, $\eta^2 = .211$). Post hoc comparisons using Tukey HSD revealed that (1) participants with MCI had significantly more misbinding error than the healthy controls ($t(33) = 2.60$, $p = .007$); and (2) both groups had significantly more misbinding error 1-sec delay than 4-sec delay ($t(33) = 1.69$, $p = .050$); and (3) both groups had significantly more misbinding error in Time1 than Time2 ($t(33) = 2.49$, $p = .009$). The finding that the misbinding error was higher in the 1-sec than 4-sec delay condition (mainly for healthy controls) appeared counterintuitive. It is likely that during the longer delay, more information was lost (see error due to guessing results) and participants had less opportunities to make misbinding errors. Participants may have also used different strategies or became more cautious, e.g., spent more time on the longer delay condition. Session by Group interaction effects were not significant ($F(1,29) = 0.79$, $p = .381$, see Figure 2C and the marginal means in Table 3). The results revealed no other significant interactions among the three factors (all ps > .05).

The results for error due to guessing revealed significant main effects of Group ($F(1,29) = 7.58$, $p = .010$, $\eta^2 = .207$), Item ($F(1,29) = 23.07$, $p < .001$, $\eta^2 = .443$), Delay ($F(1,29) = 19.45$, $p < .001$, $\eta^2 = .401$), and Session ($F(1,29) = 5.48$, $p = .026$, $\eta^2 = .159$). Post hoc comparisons using Tukey HSD revealed that (1) participants with MCI had significantly more error due to guessing than healthy controls ($t(33) = 2.44$, $p = .010$); (2) both groups had significantly more error due to guessing in 3-item condition than 1-item condition ($t(33) = 4.97$, p

< .001); (3) both groups had significantly more error due to guessing in 4-sec delay than 1-sec delay ($t(33) = 4.42$, $p < .001$); and (4) both groups had significantly more error due to guessing in Time1 than Time2 ($t(33) = 2.02$, $p = .026$). However, Session by Group interaction effects were not significant ($F(1,29) = 3.18$, $p = .085$, $\eta^2 = .099$, see Figure 2D and the marginal means in Table 3). The results revealed no other significant interactions among the four factors (all ps > .05). Participants with older age showed more errors due to guessing than those with younger age ($F(1,29) = 8.58$, $p = .007$, $\eta^2 = .228$).

The results for identification time showed significant main effects of Item ($F(1,29) = 45.47$, $p < .001$, $\eta^2 = .611$), Delay ($F(1,29) = 25.28$, $p < .001$, $\eta^2 = .466$), and Session ($F(1,29) = 9.10$, $p = .005$, $\eta^2 = .239$), but no significant main effect of Group ($F(1,29) = 1.84$, $p = .186$). Post hoc comparisons using Tukey HSD revealed that (1) both groups had significantly slower identification time in 3-item condition than 1-item condition ($t(33) = 6.74$, $p < .001$); (2) both groups had significantly slower identification time in 4-sec delay than 1-sec delay ($t(33) = 5.03$, $p < .001$); and (3) both groups had significantly slower identification time in Time1 than in Time2 ($t(33) = 2.73$, $p = .005$). Session by Group interaction effects were not significant ($F(1,29) = 0.53$, $p = .474$, see Figure 2E and the marginal means in Table 3). The results revealed no other significant interactions among the four factors (all ps > .05). Participants with older age showed slower identification time than those with younger age ($F(1,29) = 9.63$, $p = .004$, $\eta^2 = .249$).

The results for localization time showed significant main effects of Item ($F(1,29) = 46.76$, $p < .001$, $\eta^2 = .617$), Delay ($F(1,29) = 20.94$, $p < .001$, $\eta^2 = .419$), and Session ($F(1,29) = 10.63$, $p = .003$, $\eta^2 = .268$). The main effect of Group was not significant, but at a trend level ($F(1,29) = 3.29$, $p = .080$), with participants with MCI having slower localization time than the healthy controls. Post hoc comparisons using Tukey HSD indicated that (1) both groups had a significant slower localization time in 3-item condition than 1-item condition ($t(33) = 6.84$, $p < .001$); (2) both groups had a significant slower localization time in 4-sec delay than 1-sec delay ($t(33) = 4.58$, $p < .001$); and (3) both groups had significantly slower localization time in Time1 than Time2 ($t(33) = 2.94$, $p = .003$). Session by Group interaction effects was not significant ($F(1,29) = 0.58$, $p = .455$), see Figure 2F and the marginal means in Table 3). The results revealed no other significant interactions among the four factors (all ps > .05). Participants with older age showed slower identification time than those with younger age ($F(1,29) = 16.13$, $p < .001$, $\eta^2 = .357$).

Trail Making Task (TMT)

For the TMT, an ANCOVA was run to investigate the impact of Group (MCI, Healthy), Condition (Number-only, Number-letter), and Session (Time1, Time2) on task performance (i.e. error rate, reaction time). Age and sex were entered as covariates. The pattern of the results remained similar after outliers were winsorized.

The results for error rate revealed significant main effects of Condition ($F(1,29) = 7.36$, $p = .010$, $\eta^2 = .202$, $p = .080$ after outliers were winsorized), and Session ($F(1,29) = 13.63$, $p = .001$, $\eta^2 = .320$), but no significant main effect of Group ($F(1,29) = 0.54$, $p = .469$). Post hoc comparisons using Tukey HSD test suggested that (1) both groups had significantly higher error rates in Number-letter condition than Number-only condition ($t(33) = 2.44$, $p = .010$); and (2) both groups had significantly higher error rates in Time1 than Time2 ($t(33) = 3.36$, $p = .001$). Session by Group interaction effects was not significant ($F(1,29) = 2.87$, $p = .101$,

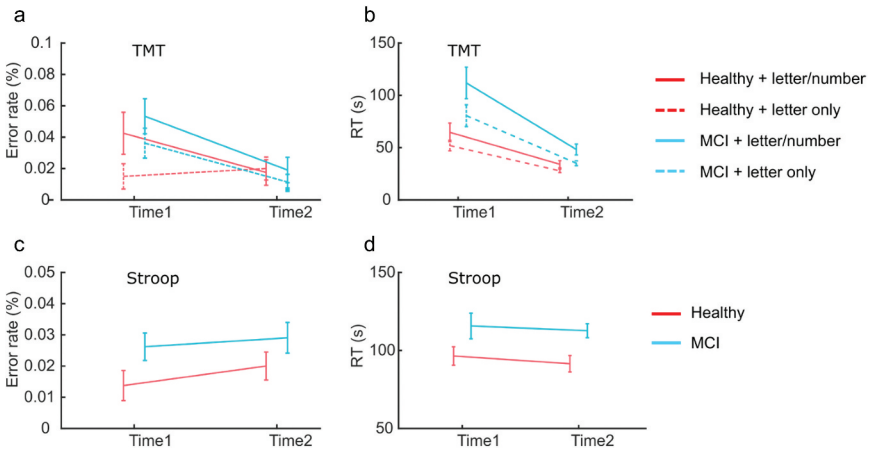

Figure 3. Results of Trail Making Task (TMT) and Stroop Task. For TMT plots (A and B), mean performance for letter-number condition (in regular line) and letter only (in dotted line) for healthy controls (red) and participants with MCI (blue). (A) TMT error rate. (B) TMT reaction time. For Stroop plots (C and D), mean performance for healthy controls (red) and participants with MCI (blue). (C) Stroop error rate. (D) Stroop reaction time. Note: Error bars represent ± standard error. Time1: pre-napping; Time2: post-napping.

see Figure 3A and the marginal means in Table 3). The results revealed no other significant interactions among the three factors (all *p*s > .05).

The results for reaction time indicated significant main effects of Group ($F(1,29) = 10.41$, $p = .003$, $\eta^2 = .264$), Condition ($F(1,29) = 20.72$, $p < .001$, $\eta^2 = .417$), and Session ($F(1,29) = 69.58$, $p < .001$, $\eta^2 = .706$). Post hoc comparisons using Tukey HSD indicated that (1) participants with MCI had significantly slower reaction time than healthy controls ($t(33) = 2.94$, $p = .003$); (2) both groups had significantly slower reaction time in Number-letter condition than Number-only condition ($t(33) = 4.55$, $p < .001$); and (3) both groups had significantly slower reaction time in Time 1 than Time 2 ($t(33) = 7.72$, $p < .001$). Session by Group interaction effects was also significant ($F(1,29) = 6.91$, $p = .014$, $\eta^2 = .192$, see Figure 3B and the marginal means in Table 3), indicating that participants with MCI had significantly slower reaction time than healthy controls in Time1 ($t(33) = 2.34$, $p = .012$), but not in Time2 ($t(33) = 0.34$, $p = .633$). Group by Condition interaction effect was at a trend level ($F(1,29) = 2.97$, $p = .096$). All other interaction effects among the three factors were not significant (all *p*s > .05). Participants with older age showed slower reaction time than those with younger age ($F(1,29) = 11.60$, $p < .001$, $\eta^2 = .286$).

Stroop Task

For the Stroop test, ANCOVA was run to investigate the impact of Group (MCI, Healthy), and Session (Time1, Time2) on task performance (i.e. error rate, reaction time). Age and sex were entered as covariates. All results remained the same after outliers were winsorized.

The results for error rate revealed not significant, but a trend level, main effects of Group ($F(1,29) = 3.26$, $p = .081$), with the participants with MCI having a higher error rate. But Session main effect ($F(1,29) = 1.89$, $p = .180$), and Session by Group interaction effects ($F(1,29) = 0.29$, $p = .597$, see Figure 3C and the marginal means in Table 3) were not

significant. Participants with older age showed a higher error rate than those with younger age ($F(1,29) = 4.39$, $p = .045$, $\eta^2 = .131$).

The results for reaction time revealed significant main effects of Group ($F(1,29) = 8.11$, $p = .008$, $\eta^2 = .218$), but no significant main effects of Session ($F(1,29) = 2.28$, $p = .142$), or Session by Group interaction effects ($F(1,29) = 0.14$, $p = .711$, see Figure 3D and the marginal means in Table 3). Post hoc comparisons using Tukey HSD indicated that participants with MCI had significantly slower reaction time than healthy controls ($t(33) = 2.54$, $p = .008$). Participants with older age showed slower reaction time than those with younger age ($F(1,29) = 13.88$, $p < .001$, $\eta^2 = .324$).

Correlation Between MoCa and Cognitive Performance

To examine whether participants' cognitive impairment had any effect on these WM and executive function measures, we conducted partial correlation analysis to investigate the association between performance scores (average score of pre- and post-napping scores) and MoCA scores by controlling for age. To obtain more reliable results, we did the analyses across all participants.

For the WM task, (1) in the 3-item 1-sec delay condition, the proportion of correct responses was significantly correlated with MoCA scores ($r = .35$, $p = .035$), indicating that participants with higher MoCA scores had higher accuracy. (2) In the 3-item 4-sec delay condition, misbinding error ($r = -.35$, $p = .039$), error due to guessing ($r = -.35$, $p = .037$), and proportion of correct response ($r = .45$, $p = .005$) were all significantly correlated with MoCA scores. Therefore, participants with higher MoCA scores performed better on this WM task, especially when the difficulty level was high.

For the Trail Making Test and the Stroop Test, there was no significant correlation between performance scores and MoCA scores.

Discussion

The present study used a WM task to capture both memory precision and associative binding and found that participants with MCI exhibited impairments in both aspects, which suggests that early memory impairment in MCI might be associated with hippocampal abnormalities. Second, participants with MCI also had slower reaction times in the TMT and Stroop task than healthy controls, which indicates that MCI is not only about memory loss, but the deficits in executive function skills that affect individuals' ability to complete tasks in daily life. Additionally, the correlation analysis between MoCA scores and WM measures further supported that participants with cognitive impairments revealed lower accuracy or more errors in general.

Comparing WM Performance in MCI and Healthy Controls

On the subject of WM, we expected participants with MCI to show worse performance, especially for the trials with a higher load and longer delay. Our results mostly confirmed our hypotheses. Participants with MCI showed lower performance on recognizing the encoded items, especially for trials with a higher load. This finding is consistent with previous studies that reported more WM deficits in participants with AD/MCI than healthy

controls (Huntley & Howard, 2010; Kirova, Bays, & Lagalwar, 2015; Liang et al., 2016). We also found that participants with MCI made more binding errors when multiple items were present. Therefore, even when item locations were correctly retained by participants with MCI, the locations can be incorrectly binded to the fractals, which is consistent with findings in AD patients (Argiris, MacPherson, Della Sala, & Foley, 2020; Pertzov et al., 2013; Pertzov, Dong, Peich, Husain, & Howe, 2012; Zokaei & Husain, 2019). Considering patients with medial temporal lobe lesions display similar impairments in binding objects with locations/scenes (Hannula, Tranel, & Cohen, 2006; Libby, Hannula, & Ranganath, 2014, 2014; Watson, Voss, Warren, Tranel, & Cohen, 2013; Zokaei & Husain, 2019), the findings indicated that the medial temporal lobe, especially the hippocampus, may play a critical role in this type of WM processing and that such brain area might be affected in participants with MCI.

In addition to recognition and binding errors, we also found that participants with MCI showed lower memory precision on item locations. That is, the distance between response locations and the targets' true locations was larger in participants with MCI than in healthy controls. Such location precision impairment was consistently found in participants with AD and patients with temporal lobe lesions (Liang et al., 2016; Pertzov et al., 2013; Zokaei & Husain, 2019). Evidence also showed that the group difference on this measure may be influenced by higher binding errors, since location errors occurred more often in groups with pathologies. After controlling for the binding error, group differences in location precision either disappeared or were significantly reduced (Pertzov et al., 2013; Zokaei & Husain, 2019). However, in the current study, we found that participants with MCI had lower location precision even in the 1-item short delay (1-sec delay) condition, which could not be contaminated by binding errors. Therefore, the current finding suggested that MCI pathology may particularly affect WM precision. Using a Sternberg partial report task, Lu, Neuse, Madigan, and Dosher (2005) also found MCI participants' iconic memory to decay much faster than healthy controls, e.g., having less than one-fourth of memory duration of healthy controls. Since the medial temporal lobe, especially the hippocampus, plays a key role in supporting detailed spatial memory (e.g., Moscovitch, Nadel, Winocur, Gilboa, & Rosenbaum, 2006; Rosenbaum, Winocur, & Moscovitch, 2001), both our findings (i.e., on misbinding and location precision) suggest impairments in medial temporal lobe functioning in MCI. Indeed, volumetric studies of hippocampal structure on both participants with AD and MCI reported significant abnormalities (Van Der Flier et al., 2002), which further indicated that the structure changes might be crucial for the deficits and may happen even in early stages of cognitive impairment (Alsop, Casement, de Bazelaire, Fong, & Press, 2008; Massa et al., 2020; Rodriguez et al., 2000).

Participants with MCI also exhibited more complete forgetting of location information of the fractals, reflected by more errors due to guessing. As for response time, although older participants took longer to identify targets and find their locations, participants with MCI only showed a trend level slower localization time, compared to healthy controls. Therefore, response time measures may mainly reflect a general aging trend and are not as sensitive as other accuracy-based WM measures in differentiating the two groups. We note that group differences were not confounded by age, since age was entered as covariate in our analysis. Further, there was an age-related performance decline for almost all the WM measures used in this study (except for misbinding), which was consistent with the WM aging literature

(e.g., Park et al., 2002; Reuter-Lorenz et al., 2000), which supported the validity and sensitivity of the task used in this study.

Comparing TMT and Stroop Performance in MCI and Healthy Controls

For the TMT task, our findings supported the hypothesis that participants with MCI showed slower reaction times (although not higher error rate) when compared to healthy controls. Furthermore, both groups showed slower reaction times in the number-letter condition than the number-only condition. The condition by group interaction was at a trend level, suggesting that the number-letter condition may be more challenging to the MCI compared to the healthy controls. These findings were in line with literature suggesting that TMT trials were able to distinguish between MCI and Healthy participants (Bastug et al., 2013; Chen et al., 2013), which further indicated that participants with MCI might experience deficits in attention control (Saunders & Summers, 2010) and motor-performance (Kluger et al., 2008). Studies showed that focal attention and divided attention are particularly vulnerable in AD (Amieva, Phillips, Della Sala, & Henry, 2004; Collette & Van der Linden, 2004; Silveri, Reali, Jenner, & Puopolo, 2007), and that attentional deficits appeared at a fairly early stage of cognitive impairment (Silveri, Reali, Jenner, & Puopolo, 2007). Moreover, studies also suggested that participants with MCI often have difficulty in alternating attention when the levels of attention processing are beyond the most basic of tasks (Cullum & Lacritz, 2009). Consistent with previous findings in AD, the current findings complemented prior work with MCI and demonstrated that participants with MCI expressed more significant deficits in the number-letter condition which involves more intensive attentional switching.

As hypothesized, we found that participants with MCI experienced slower reaction time in Stroop trials and the error rate difference was marginally significant. This was consistent with previous findings that executive functions such as inhibitory control and cognitive flexibility were impaired from even early stages of Alzheimer's disease (Levy et al., 2002). The Stroop task is one of the frequently used paradigms to evaluate the management of conflict and the inhibition of automatic responses (Stroop, 1992). Studies further confirmed that Stroop task, compared to other similar tasks, e.g., Wisconsin Card Sorting Test (Milner, 1963), or Flanker Task (Eriksen & Eriksen, 1974), seemed to be the most effective paradigm for discriminating between AD patients and normal-aging elders (see review by Guarino et al., 2019). More recent studies reported that Stroop task became more commonly used in clinical assessment and was shown to have a high discriminative ability between participants with and without MCI (Bélanger, Belleville, & Gauthier, 2010; Chen et al., 2013; Johns et al., 2012). In addition, Alsop et al. (2008) found that there was a partial preservation of goal maintenance abilities in participants MCI, thus by reducing response speed they could still maintain a level of error rate that was more similar to healthy controls. Our findings further supported that the Stroop task might be valuable for diagnosing early stages of cognitive impairments, and such impairment might be more significant in reaction time than error rate.

Pre- and Post-Napping Changes and Executive Functions

Given that we did not design the study as an intervention trial and the napping effect is only an exploration question for the current study, caution is required when interpreting the

results related to pre- and post-napping cognitive performance changes. We largely observed that both groups showed similar post-nap improvements in WM and executive function performance. Based on the current design, we cannot specify to what extent the post-napping performance changes were due to napping *per se* or/and practice effects. Future studies are needed to further examine how napping or sleep affects WM and other executive functions in such groups. Considering that all major WM measures derived from the OMT task did not show differential changes before and after napping between the two groups, it is reasonable to infer that WM binding and precision in participants with MCI were likely not differentially affected by napping when compared to healthy peers, and that the WM measured used in the present study was potentially both reliable and sensitive for diagnosis of early cognitive impairment.

Limitations

We noted that the current study had a relatively small sample size. Therefore, we need to be cautious drawing firm conclusions with respect to the null findings, especially regarding the napping effect. Also, the MCI group in the current study was not diagnosed formally through clinical interview. Although using a MoCA score of 26 as the cutoff to identify participants with MCI had adequate specificity and sensitivity (Nasreddine et al., 2005), we cannot exclude the possibility that some participants' cognitive impairment may not be severe enough for a formal MCI diagnosis. None of the participants had a diagnosis of dementia. All were able to interact with experimenters and understand instructions for the tasks. They completed physical and mental well-being questionnaires independently. However, we examined group differences specifically on MoCA memory scale and the Rey Auditory Verbal Learning Test (RAVLT) delayed-recall scores (see Appendix I) and the results of MCI showed significantly worse performance than healthy controls, which further confirmed memory deficits in MCI. Also, the mean RAVLT delayed-recall score of the MCI group in our study closely matched the U.S. nationwide data (Loring et al., 2016).

In summary, the current study found that participants with MCI were deficient in not only the quantity in WM (e.g., accuracy rate), but also in the quality of their memory (e.g., memory binding and location precision). On the whole, napping had no differential effects on these WM measures, further suggesting that the OMT task can provide reliable WM measures to differentiate participants with MCI from healthy controls, and may be used in clinical assessment to increase the sensitivity of detecting different WM symptoms.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Appendix I

Rey Auditory Verbal Learning Test (RAVLT)

The Rey Auditory Verbal Learning Test (RAVLT) is a neuropsychological tool used to assess memory functions (Lezak, Howieson, Loring, & Fischer, 2004; Malloy-Diniz, Lasmar, Gazinelli, Fuentes, & Salgado, 2007). There are two lists of words presented as targets: List A and List B. The procedure of administration was as follows: List A was presented four times for immediate recall after each presentation (trials I, II, III, IV), List B was presented (trial V), and then List A was presented fifth time (trial VI). After 0 min of trial VI was presented, the participants were asked to recall List A without a previous presentation (delayed-recall). The number of successful delayed-recalls was recorded as delayed-recall score.

We analyzed the delayed-recall scores for the two groups. Two participants in the MCI group and two participants in the healthy group were removed from the analysis due to incomplete responses. An ANCOVA was conducted to compare the two groups with age entered as covariate. The results showed significant Group effect, $F(1,30) = 6.19$, $p = .019$, $\eta^2 = .171$. The healthy control group (mean = 5.9, $SD = 3.7$) performed significantly better than the MCI group (mean = 2.9, $SD = 3.5$). We also note that the MCI group's performance on this task closely matched that of a large MCI sample in the United States (mean = 2.9, $SD = 3.3$; Loring et al., 2016).