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性別差異於認知老化與阿茲海默症早期偵測之研究 (L03)(第3年)

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本研究具有政策應用參考價值：■否 □是，建議提供機關
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本研究具影響公共利益之重大發現：□否 □是

中　華　民　國　113　年　01　月　25　日

中 文 摘 要 ： 許多的神經退化疾病，例如阿茲海默症，腦與心智功能上的改變在正式被診斷之前多年就可能露出一些端倪。因此，本計劃透過招募健康與輕度認知受損高齡受試者，收集多向度的資料(例如神經心理評估，失智相關風險因子資料的收集、腦影像資料)，來探討秤常與異常老化過程的性別差異性。透過記憶典範，我們發現在健康高齡者中，女性在立即性回憶之項目與聯結性記憶具有優勢，而且在聯結性記憶的優勢即使是在控制項目記憶下仍舊存在。相比之下，在aMCI患者中，女性並沒有這種優勢；這些女性比患有aMCI的男性更容易產生聯結記憶的錯誤。此外，與性別匹配的對照組相比，患有aMCI的個體中的項目記憶、聯結記憶和皮質厚度的下降在女性中比男性更為明顯，特別是在perirhinal 和 entorhinal區域。腦結構與聯想記憶功能之間的聯繫僅對女性而言是明顯的，表明女性和男性可能在處理聯想記憶的認知和神經機制方面存在差異。而透過靜息式核磁共振造影資料的分析，我們也發現男性與女性高齡者，在區辨正常與異常高齡者時，不同的腦區具有不同的區辨度。這些發現在相關領域文獻中都具有創新性，然而由於樣本相對較小，所的結果仍需更多後續研究來驗證。

中 文 關 鍵 詞 ： 正常老化;輕度認知受損;認知功能;性別;大腦

英 文 摘 要 ： Many neurodegenerative diseases, such as Alzheimer's disease, may exhibit changes in brain and cognitive functions years before formal diagnosis. Therefore, this project recruited healthy older adults and older adults with mild cognitive impairment (MCI), collecting multidimensional data (e.g., neuropsychological assessments, collection of dementia-related risk factor data, brain imaging data) to explore sex differences in normal and abnormal aging processes. Through a memory paradigm, we found that in healthy older individuals, females have advantages in immediate item and associative memory, and the advantage in associative memory persists even after controlling for item memory. In contrast, in individuals with amnestic MCI (aMCI), females did not show this advantage; these females were more prone to associative memory errors compared to males with aMCI. Furthermore, the decline in item memory, associative memory, and cortical thickness in individuals with aMCI versus their gender-matched controls was more pronounced in females, especially in the perirhinal and entorhinal regions. The connection between brain structure and associative memory function was evident only for females, suggesting cognitive and neural mechanism differences between males and females in processing associative memory. Through the analysis of resting-state functional magnetic resonance imaging data, we also found that older males and females have different brain regions with distinct discriminative power in distinguishing normal from abnormal

aging. These findings contribute innovative insights to the relevant literature; however, due to the relatively small sample size, further research is needed to validate the results.

英文關鍵詞：Normal aging, mild cognitive impairment, cognitive function, sex, brain

Amnestic mild cognitive impairment (aMCI), characterized by episodic memory deficits and medial temporal regional atrophy, is a well-established risk factor for the development of dementia, particularly Alzheimer disease (AD) [1]. Studies have examined several factors explaining interpersonal differences in the episodic memory decline of individuals with aMCI or between individuals with aMCI and cognitively healthy older adults (HOs). Among these various factors, considerable attention has been given to sex-specific differences in MCI. Studies have revealed a sex effect on cognitive function and the trajectory of cognitive decline [2-5]. For example, although the results have been inconsistent, some studies have revealed that compared to men with aMCI, women with aMCI exhibited greater cognitive and functional decline and progressed to AD more rapidly when age was adjusted [4, 6]. These findings are consistent with the concept of cognitive reserve [7], which predicts that once brain pathology depletes brain resources past a threshold level, cognitive impairments become apparent and are more accelerated in persons with high reserve than those with low reserve because the pathology is more advanced at that point. Similarly, consistent with the pattern observed in patients with AD [6], cognitive differences in memory between female HOs and women with MCI were reportedly greater than those between male HOs and men with MCI [8], suggesting that such declines are more rapid in women than in men after an aMCI diagnosis. Given that aMCI may represent an early-stage deviation from the normal aging process, investigating the extent of memory deficits associated with sex differences may be crucial to understanding individual differences in cognitive deficits during the development of dementia and evaluating dementia risks among individuals with aMCI.

Verbal episodic memory research has demonstrated a female advantage in verbal episodic memory tasks among HOs [9, 10], and studies have revealed that men had greater age-related declines than women in verbal episodic memory tests [9, 11]. Evidence for female benefits in verbal episodic memory is largely based on findings from word list recall tests, and in these tests, such benefits have been identified across multiple studies [2, 8, 12-15]. However, divergent findings have been observed in studies that have used word pair associative tasks; some studies have provided findings supporting these female benefits [15-17], whereas others have not identified a sex difference [18, 19]. In contrast to the many studies on HOs, studies concerning sex differences in verbal memory among people with aMCI are relatively scarce, and the results have been inconsistent. Some studies have reported that individuals with MCI had a female advantage indicated in word list recall tests [2, 14]. Other studies, however, have reported no sex differences in word list recall tests [8, 19, 20]. Only one study, which had a small sample size, examined sex differences in the associative memory of people with MCI by using a face–name associative task, but no difference was observed [19].

The reasons for the different results between HOs and people with MCI remain unclear, and studies on MCI have had several design limitations that hinder the interpretation of results. First, studies have revealed that compared with HOs, individuals with amnestic MCI due to atrophy in the hippocampal formation, including in the entorhinal regions, which are critical for establishing associations between components of memory episodes [21], had greater deficits in associative memory relative to item memory [22, 23]. This difference between associative and item memory is particularly evident when tests employ a recognition format, given that associative memory recognition, unlike item memory recognition, cannot be performed through a familiarity process [24]. However, all these studies involving people with MCI have not conjunctionally

measured or compared item and associative memory performance in the same individual; thus, whether the relative changes in item versus associative memory are associated with sex differences in populations with MCI remains unknown. Second, individuals with aMCI may experience impaired immediate learning and delayed recall [25], but evidence suggests that individuals with aMCI may be vulnerable to memory consolidation deficits because delayed recall deficits in individuals with MCI relative to healthy controls remained even when groups were carefully matched based on initial learning [26, 27]. The effect of sexual dimorphism on differences in immediate versus delayed recall in individuals with MCI has been examined by using word list learning [2, 8, 14, 19], but the results have been inconsistent. For example, one study reported that compared to men with MCI, women with MCI exhibited greater impairment in both immediate and delayed word list recalls relative to their sex-matched controls, and the gap in delayed recall performance was larger compared to immediate recall performance [8]. Other studies, however, have indicated that women with MCI outperformed men with MCI in both immediate learning and delayed recall in word list recall tests [2, 14]; in another study, women with MCI outperformed men with MCI in immediate recall, but no sex effect was observed in delayed recall performance [19]. No study has investigated sex differences in immediate versus delayed recall in associative memory tasks. Third, although the link between medial temporal atrophy and memory decline is well established in individuals with MCI, it remains unknown whether sexual dimorphism modulates this effect.

To address the aforementioned research gaps, this study investigated the sex-specific differences in item and associative memory of HOs and individuals with aMCI. The present study had two aims. First, we examined potential sex differences in verbal episodic memory through a word associative memory task. Specifically, we assessed patterns of item versus associative memory performance in HOs and individuals with MCI in a sex-dependent fashion. We also examined the effect of immediate and delayed recall given that delayed recall measures may be more sensitive for detecting differences between HOs and individuals with MCI [22]. We hypothesized that a female advantage would be observed in item and associative memory of HOs. On the basis of previous studies [4, 6, 8], we further hypothesized that the female advantage in both item and associative memory would be absent in women with aMCI and that memory differences between women with MCI and female HOs would be greater than those between men with MCI and male HOs, indicating that women with aMCI would have greater memory impairments, relative to controls, than would men with aMCI. We also expected that the aforementioned group differences would be greater for associative memory relative to item memory as well as for delayed memory relative to immediate memory because evidence has suggested that individuals with aMCI have poorer associative memory relative to item memory [22, 23] as well as poorer delayed recall or memory retention relative to immediate learning [22, 25] due to medial temporal atrophy. Second, we examined the associations between morphometric measures of medial temporal structures (i.e., hippocampus, parahippocampus, and perirhinal/entorhinal regions) and potential sex effects on item and associative memory. Because it is well established that the hippocampus is crucial for binding and recollecting new item–item associations in associative memory [24], we expected that variations in the gray matter morphometric measures of medial temporal regions, particularly the hippocampus, may account for the greater interpersonal differences in associative memory compared with item memory in older adults with and without MCI.

Materials and methods

Participants

The study sample initially consisted of 60 older adults (30 women and 30 men) with MCI and 60 HOs (30 women and 30 men). However, 11 participants with MCI and 5 HOs were excluded from the current study due to the following reasons: 1) unable to complete the behavioral sessions; 2) contraindications for magnetic resonance imaging (MRI) scan. The final sample consisted of 49 MCI (25 women, 24 men) and 55 HOs (34 women, 21 men). Participants were classified into four groups: Female HO (F-HO), Male HO (M-HO), Female MCI (F-MCI), and Male MCI (M-MCI). The participants with MCI were recruited from memory clinics at local hospitals, and the HOs were recruited from nearby residential communities. Potential participants were thoroughly screened through interviews to exclude individuals with a current or past diagnosis of a neurological or psychiatric disorder, a known head injury with loss of consciousness, contraindications for magnetic resonance imaging (MRI), alcohol or substance abuse, any severe visual or auditory impairment precluding participation in neuropsychological testing, or extensive white matter hyperintensities on structural MRI. The present study was approved by the Institutional Review Board of National Taiwan University Hospital. Written informed consent was obtained from all participants. Table 1 presents participants' demographic and clinical characteristics.

Table 1
Demographic and clinical characteristics of female (F) and male (M) participants in the healthy older adult (HO) and mild cognitive impairment (MCI) groups.

	F–HO (n = 34) Mean (SD)	M-HO (n = 21) Mean (SD)	F-MCI (n = 25) Mean (SD)	M-MCI (n = 24) Mean (SD)	*P value*
Age (years)	71.59 (4.59)	73.29 (5.28)	73.84 (7.20)	74.67 (5.98)	.22
Education (years)	12.71 (2.30)	14.05 (2.27)	12.28 (2.61)	13.46 (3.38)	.11
MMSE	28.10 (1.86)	28.22 (1.67)	26.35 (2.25)	27.00 (1.56)	$F_{(3,103)} = 4.96$, $p = .003$[ab]
aMCI single domain/aMCI multidomain	–	–	10/15	10/14	.57
FSRP % stroke risk	13.15 (13.25)	16.90 (7.71)	19.08 (15.44)	17.13 (9.31)	.29
Hypertension history (%)	46	56	50	68	.50
ApoE e4 + (%)	32	35	53	47	.47
Geriatric depression scale	2.76 (2.72)	3.81 (4.12)	2.84 (2.61)	3.17 (3.60)	.67
CDR-SB	0.50 (0.67)	0.35 (0.33)	1.25 (1.36)	0.81 (0.92)	$F_{(3,103)} = 4.35$, $p = .007$ [c]

Notes: ApoE, apolipoprotein E; CDR-SB, sum of boxes scores on the Clinical Dementia Rating scale; FSRP, Framingham Stroke Risk Profile; HOs, healthy older adults; MCI, mild cognitive impairment. MMSE, Mini-Mental State Examination. Note: All scores are raw scores for cognitive measures. For brain measures, all regions were averaged across right and left hemispheres. *P* indicates the results of overall (four-group) comparisons; *a* indicates a significant difference between the F–HO group and the two aMCI groups; *b* indicates a significant difference between the M-HO and the two MCI groups; *c* indicates a significant difference between the two HO groups and the F-MCI group.

The participants were classified as having MCI according to criteria adapted from Petersen and Morris [28]. The criteria were as follows: (1) normal activities of daily living, (2) absence of dementia, and (3) mild quantifiable cognitive impairment in one or more domains. The criterion of objective cognitive impairment was operationally defined as a performance score ≥ 1 standard deviation (SD) lower than the age-appropriate norm on at least two measures in at least one cognitive domain[29]. According to the aforementioned criteria, the MCI sample in the present study was comprised of 20 participants (10 women, 10 men) with impairment in only episodic memory [i.e., single-domain amnestic

MCI (S-aMCI)] and 29 participants (15 women, 14 men) with impairments in memory and other cognitive function domains [i.e., multidomain amnestic MCI (M-aMCI)].

Neuropsychological evaluation

All the participants underwent a neuropsychological battery test assessing cognitive functioning in four domains, namely attention/visuomotor processing speed, language, episodic memory, and executive function. The four neuropsychological domains were assessed using the following tests: (1) attention: standardized Taiwanese versions of the Digit Span Forward length and Digit Symbol Substitution (DSS) of the Wechsler Adult Intelligence Scale, Third Edition (WAIS-3) [30]; (2) language: the category fluency test (animal) and the 30-item Boston Naming Test [31]; (3) learning and memory: the logical memory (LM) and visual reproduction (VR) subtests of the Wechsler Memory Scale-III (WMS-3) [32] and the California Verbal Learning Test-II (CVLT-II)[33]; and (4) executive function: the Design Fluency Test (switching condition) of the Delis–Kaplan Executive Function System (D-KEFS) [34] and the letter-number sequencing subtest of the WAIS-3. In addition to these cognitive test scores, the Mini-Mental State Examination (MMSE), Clinical Dementia Rating Scale (CDR) [35], Geriatric Depression Scale (GDS) [36], and the Framingham Stroke Risk Profile (FSRP) [37] scores of all participants were obtained to evaluate their overall cognitive function, global functional status, depressive symptoms, and cerebrovascular risk burden, respectively.

Word association task

Details on the word association task used were described in our previous work [22]. In brief, this task involves a visual presentation of a list of eight semantically unrelated Chinese character pairs. Each pair was presented for a total of 4 seconds over three learning trials. After the learning phase, immediate item and associative recognition tests with a yes (target)/no (foil) forced choice format were administered, followed by a 30-minute delayed item recognition test and an associative recognition test. The recognition tests were self-paced. The item recognition trial consists of 16 target items and 16 foils. The associative recognition test had 48 trials, comprising 8 trials for original pairs and 8 trials for each of the following 5 foil types: (1) recombined pairs: characters from the learned pairs that have been recombined; (2) orthographically related pairs: a visually similar character with the same structure and common component [38, 39] was substituted for one of the originally paired characters; (3) phonologically related pairs: a homophone Chinese character [40] was substituted for one of the originally paired characters pairs; (4) semantically related pairs: a character with a strong semantic relationship (i.e., a synonym) with an originally paired character was substituted for it [41]; and (5) novel pairs: one character in the original pairs was replaced by a new character that had not been presented previously and did not belong to the aforementioned categories of foils. Relevant features (i.e., word frequency, level of concreteness, strokes counts, neutral emotional valence) were matched among the character pairs. Different sets of foils for immediate and delayed recognition tests were used, and the order of the foil substitution for each set of paired stimuli was counterbalanced among the trials.

Word association task index calculations

The discriminability (*d'*), hit rate, and total false alarm (FA) rate generated from both the item and associative recognition tests were used for analyses. To calculate *d'*, the hit rate and FA rate were first converted into *z*-scores and subsequently calculated using the formula $d' = Z(\text{hit rate}) - Z(\text{false alarm rate})$, with an adjusted score used for extreme values (i.e., hit rate = 100%; FA rate = 0%).

MRI data acquisition and processing

The brains of all the participants were scanned using a 3-T MRI system (Magnetom Trio; Siemens, Erlangen, Germany) featuring a 32-channel phased-array head coil. The section orientation of the T1-weighted images was parallel to the anterior–posterior commissure line. High-resolution T1-weighted images were obtained using a 3D magnetization-prepared rapid gradient echo sequence (coronal slicing; repetition time/echo time = 2000/2.98 ms; flip angle = 9°; field of view = 256 × 192 × 208 mm^3; matrix size = 256 × 192 × 208; voxel size = 1 × 1 × 1 mm^3).

The T1-weighted images were reviewed for quality. The imaging data of seven participants (3 F-HO, 1 M-HO, 1 F-MCI, and 2 M-MCI) were excluded from further data analysis due to head motion. The data of all other participants were then processed using the FreeSurfer analysis suite (Version 6.0; Martinos Center for Biomedical Imaging, Charlestown, MA, USA). The processing comprised cortical reconstruction and subcortical segmentation [42, 43], as well as parcellation of the cerebral cortex into regions of interest (ROIs) [44, 45]. The ROIs were confined to medial temporal structures given that our primary focus was on memory function. In these ROIs, we measured bilateral hippocampal volumes, parahippocampus thickness, and perirhinal/entorhinal (PRC/EC) thickness. Additionally, we also collected resting-state functional MRI, the imaging parameters were echo planar imaging volumes = 180, TR/TE = 2000/24 ms, flip angle = 90°, FOV = 256 x 256 mm2, matrix size = 64 x 64, slice thickness = 3 mm, voxel size = 4 x 4 x 3 mm3. All participants were instructed to remain still with their eyes closed to complete a 6-min resting-state fMRI scan.

Statistical analyses

Analyses of variance (ANOVA) or chi-squared tests were used to compare group demographic (i.e., age and education attainment) and clinical data (i.e., MCI subtype distribution, CDR sum of boxes scores, FSRP scores, hypertension history, proportion of apolipoprotein E e4 carriers, and GDS scores) at an α level of .05. For group comparisons on standardized neuropsychological variables, we used univariate ANOVAs, reported as significant at the threshold of $p < .0042$ (Bonferroni correction). Using Cohen's *d*, effect sizes were calculated for pairwise comparisons of significant neuropsychological variables [46].

For the word association task performance, separate ANOVAs with repeated measures were performed to determine the *d*', hit rate, and FA rate for each of the item and associative memory tasks, with time (immediate and delayed) treated as a within-subject variable and group treated as a between-subject variable. Moreover, to determine whether associative memory was disproportionately impaired relative to item memory between groups, the immediate and delayed item *d'* were regressed out from associative *d'* for the immediate and delayed recall conditions, respectively, before repeated measures ANOVAs were conducted. To further evaluate changes relative to sex-matched healthy controls, the item and associative memory performance scores of each individual in the two MCI groups were converted into z-scores based on the mean and SD obtained from their sex-matched controls. The α level concerning association task performance was set at $p < .05$ for each mixed ANOVA model.

To assess group differences in morphometric variables, the effect of age was first regressed from all thickness and volumetric measures. Additionally, we corrected hippocampal volume for differences in head size by regressing out the estimated total intracranial volume (eTIV) [47]. Because the current study did not propose hypotheses on hemispheric effects and to decrease the number of comparisons, the volumes and

cortical thickness variables were averaged across right and left hemisphere values to decrease the number of comparisons. Standardized residual values (*z*-scores) were employed for all relevant analyses, with the α level set at .017 (Bonferroni adjustment). The association between item and associative memory performance and the medial temporal lobe brain variables were examined through Pearson product–moment correlations for all participants and separately for the two sex groups. The α level was set at $p < .0125$ based on Bonferroni corrections by using the per-family error rate ($\alpha_{PF} = .05$) divided by the number of correlational comparisons as the significance threshold for analyses concerning each brain variable.

Results

Demographic, clinical, and cognitive characteristics by group

The four groups did not significantly differ in age, education level, FSRP score, hypertension history, proportion of apolipoprotein E (ApoE) e4 carriers, or GDS score (Table 1). As expected, the two HO groups had significantly higher MMSE scores than did the two MCI groups. The two MCI groups had comparable CDR sum of boxes scores, and the F-MCI group, but not the M-MCI group, had higher scores than did the two HO groups (both $p < .005$). The frequency distribution of subtypes of amnestic MCI (e.g., single domain vs. multidomain) did not differ between the two MCI groups.

On the standardized neuropsychological measures (Table 2), the four group comparisons reached significance in the DSS test, all six memory related measures, and the two executive function measures (all $p < .0042$). Specifically, the post hoc analyses revealed a risk factor (i.e., with vs. without MCI) effect (i.e., F-HO = M-HO > F-MCI = M-MCI) across all these measures, and no sex difference was noted within the HO or MCI cohorts. The F-HO group outperformed both the F-MCI and M-MCI groups in DSS score ($p < .001$, Cohen's $d = 1.21$ vs. $p < .001$, Cohen's $d = 1.02$), LM immediate score ($p < .001$, Cohen's $d = 1.42$ vs. $p < .001$, Cohen's $d = 1.06$), LM delayed score ($p < .001$, Cohen's $d = 1.50$ vs. $p < .001$, Cohen's $d = 1.21$), VR immediate score ($p < .001$, Cohen's $d = 1.05$ vs. $p = .006$, Cohen's $d = 0.85$), VR delayed score ($p < .001$, Cohen's $d = 1.52$ vs. $p < .001$, Cohen's $d = 1.54$), CVLT-II total learning ($p < .001$, Cohen's $d = 2.44$ vs. $p < .001$, Cohen's $d = 3.04$), CVLT-II long delayed free recall score ($p < .001$, Cohen's $d = 2.31$ vs. $p < .001$, Cohen's $d = 3.17$), letter-number sequencing score ($p < .001$, Cohen's d

Table 2
Cognitive and brain morphometric characteristics of female (F) and male (M) participants in the healthy older adult (HO) and mild cognitive impairment (MCI) groups.

	F-HO Mean (SD)	M-HO Mean (SD)	F-MCI Mean (SD)	M-MCI Mean (SD)	*P* value (two-tailed)
Digit span forward length	7.76 (1.16)	7.38 (1.16)	7.52 (1.42)	7.46 (1.22)	.67
Digit symbol substitution	62.21 (15.01)	57.86 (13.54)	44.64 (14.07)	46.71 (15.50)	$F_{(3,103)} = 9.43$, $p < .001$ [ab]
Category verbal fluency	31.00 (5.68)	31.19 (7.10)	27.64 (6.20)	26.33 (7.40)	.017
Boston naming test-short	28.44 (1.78)	28.67 (1.71)	26.60 (3.19)	27.88 (2.13)	.008
LM immediate recall	41.56 (10.94)	40.52 (10.44)	25.80 (11.18)	29.33 (12.07)	$F_{(3,103)} = 13.30$, $p < .001$ [ab]
LM delayed recall	26.35 (8.29)	25.48 (9.38)	13.52 (8.85)	15.67 (9.32)	$F_{(3,103)} = 14.60$, $p < .001$ [ab]
VR immediate recall	76.74 (18.68)	78.61 (10.83)	57.83 (17.44)	62.39 (14.85)	$F_{(3,103)} = 7.93$, $p < .001$ [ab]
VR delayed recall	62.36 (14.99)	58.44 (26.04)	28.78 (27.45)	32.78 (22.72)	$F_{(3,103)} = 10.88$, $p < .001$ [ab]
CVLT-II total learning	52.44 (8.82)	45.71 (10.11)	32.00 (7.93)	27.67 (7.41)	$F_{(3,103)} = 50.50$, $p < .001$ [ab]
CVLT-II long delayed free recall	12.03 (2.41)	10.29 (3.33)	4.32 (4.07)	3.79 (2.78)	$F_{(3,103)} = 48.04$, $p < .001$ [ab]
Letter number sequencing	9.38 (2.53)	8.90 (2.30)	6.38 (2.42)	6.43 (3.19)	$F_{(3,103)} = 8.47$, $p < .001$ [ab]
Design fluency-switching	6.38 (1.69)	6.38 (1.72)	4.80 (2.72)	4.67 (1.97)	$F_{(3,103)} = 5.59$, $p = .001$ [ab]
Raw hippocampal volume (mm^3)	3383.68 (366.01)	3651.69 (358.02)	3194.61 (470.28)	3297.36 (363.23)	$F_{(3,103)} = 3.71$, $p = .015$ [ab]
Hippocampal volume controlled for eTIV and age (z-score)	0.20 (0.89)	0.46 (0.83)	−0.31 (1.13)	−0.33 (0.72)	$F_{(3,103)} = 3.71$, $p = .015$ [ab]
Raw parahippocampal thickness (mm)	2.66 (0.26)	2.56 (0.18)	2.59 (0.18)	2.59 (0.31)	.47
Raw PRC/EC thickness (mm)	3.28 (0.21)	3.16 (0.29)	3.13 (0.27)	3.19 (0.30)	.19

= 1.21 vs. $p < .001$, Cohen's $d = 1.02$), and design fluency switching condition score ($p = .004$, Cohen's $d = 0.70$ vs. $p = .002$, Cohen's $d = 0.93$).

Similarly, the M-HO group outperformed both the F-MCI and M-MCI groups in the DSS score ($p < .001$, Cohen's $d = 0.96$ vs. $p < .001$, Cohen's $d = 0.77$), LM immediate score ($p < .001$, Cohen's $d = 1.36$ vs. $p < .001$, Cohen's $d = 0.99$), LM delayed score ($p < .001$, Cohen's $d = 1.31$ vs. $p < .001$, Cohen's $d = 1.05$), VR immediate score ($p < .001$, Cohen's $d = 1.43$ vs. $p = .006$, Cohen's $d = 1.25$), VR delayed score ($p < .001$, Cohen's $d = 1.11$ vs. $p < .001$, Cohen's $d = 1.05$), CVLT-II total learning score ($p < .001$, Cohen's $d = 1.51$ vs. $p < .001$, Cohen's $d = 2.04$), CVLT-II long delayed free recall score ($p < .001$, Cohen's $d = 1.60$ vs. $p < .001$, Cohen's $d = 2.12$), letter number sequencing score ($p < .001$, Cohen's $d = 1.07$ vs. $p < .001$, Cohen's $d = 0.89$), and design fluency switching score ($p = .004$, Cohen's $d = 0.69$ vs. $p = .002$, Cohen's $d = 0.93$).

In summary, the four groups exhibited similar demographic (i.e., age, education level) and clinical (i.e., cerebrovascular risk burden, ApoE status, depressive symptoms) characteristics, except for their cognitive status. Furthermore, the two MCI groups demonstrated a similar level of cognitive function across standardized neuropsychological measures that evaluate global cognitive function, attention/ visuomotor processing speed, language, episodic memory, and executive function.

Word association task performance

Item memory

We observed a significant group effect ($F_{(3, 99)} = 14.90$, $p < .001$, partial $\eta^2 = 0.32$), time effect ($F_{(1, 99)} = 16.50$, $p < .001$, partial $\eta^2 = 0.15$), and group-by-time interaction ($F_{(3, 99)} = 4.32$, $p = .007$, partial $\eta^2 = 0.12$) for item *d'* (Figure 1A). Specifically, the F-HO group had better item memory under the immediate recall condition compared with the M-HO ($p = .014$, Cohen's $d = 0.68$), F-MCI ($p < .001$, Cohen's $d = 1.40$), and M-MCI ($p = .001$, Cohen's $d = 0.90$) groups; the M-HO group also outperformed the F-MCI group ($p = .019$, Cohen's $d = 0.72$), but not M-MCI group, and the two MCI groups had similar performance. After a 30-minute delay, the F-HO group outperformed the F-MCI ($p < .001$, Cohen's $d = 1.47$) and M-MCI ($p < .001$, Cohen's $d = 1.35$) groups; the M-HO groups outperformed the F-MCI ($p < .001$, Cohen's $d = 1.13$) and M-MCI ($p = .001$, Cohen's $d = 1.02$) groups, and no sex difference was noted within the HO or MCI cohorts. The M-MCI group, but not the F-MCI group, showed significantly greater reduction in item memory discriminability over time compared to the F-HO ($p = .01$, Cohen's $d = 0.70$) and M-HO ($p = .001$, Cohen's $d = 1.30$) groups. Relative to their sex-matched controls, the F-MCI group exhibited greater impairment in immediate item *d'* ($T_{(47)} = -4.30$, $p < .001$, Cohen's $d = -1.24$) than did the M-MCI group, but the two MCI groups exhibited similar impairment in delayed item memory (Figure 1B).

In terms of item memory hit rate (Table 3), a main effect of time ($F_{(1, 99)} = 8.08$, $p = .005$, partial $\eta^2 = 0.78$) was observed, with a lower hit rate in the delayed recall condition than in the immediate recall condition; no main effect of group or group-by-time interaction was observed. Relative to their sex-matched controls, the F-MCI group had a poorer item hit rate compared with the M-MCI group ($T_{(47)} = -2.39$, $p = .021$, Cohen's $d = -0.69$) in the immediate recall condition, but no difference between the two groups was detected in the delayed recall condition.

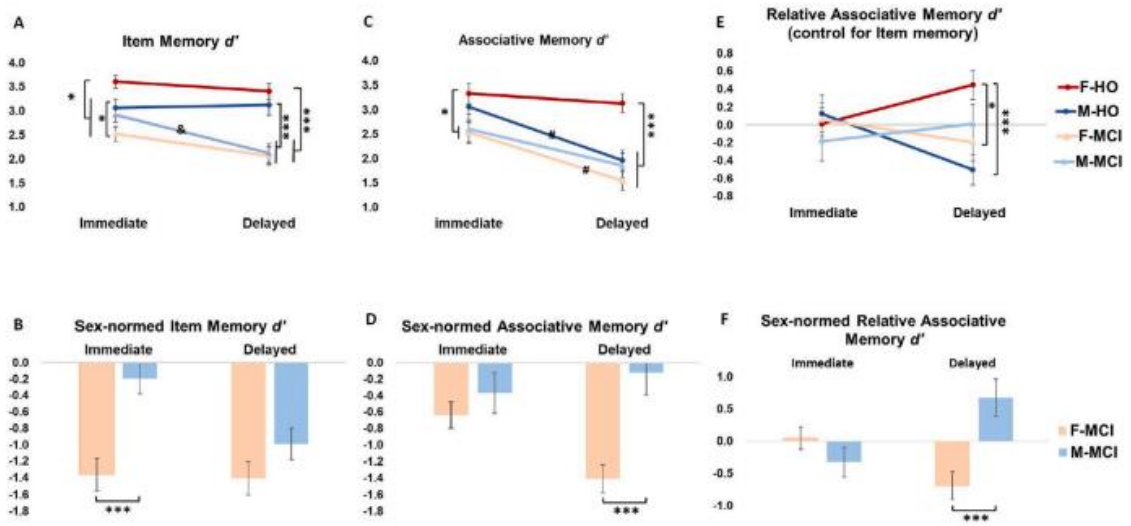

Fig. 1. Word association task performance among groups for immediate and delayed recall conditions: (A) Item memory discriminability (d') for four groups, (B) relative item memory d' for the two mild cognitive impairment (MCI) groups compared with their sex-matched controls indicated by *z*-scores, (C) associative d' for four participant groups, (D) relative associative d' for the two MCI groups compared with their sex-matched controls indicated by *z*-scores, (E) associative d' based on residual values (*z*-scores) after the effect of the corresponding item recognition d' was removed for four groups, (F) relative associative d' for the two MCI groups compared with their sex-matched controls (*z*-scores) after control for corresponding item d'. Error bars denote standard deviations.*$p < .05$; ***$p < .005$. F–HO = female-health older adults; M-HO = male-healthy older adults; F-MCI = female-MCI; M-MCI = male-MCI. [&] denotes the slope of item memory decays in the M-MCI group significantly differ from that in the two HO groups. [#] denotes slopes of associative memory decays in the M-HO and F-MCI significantly differ from that in the F–HO group.

With respect to FA rate, significant main effects of group ($F_{(1, 99)} = 7.80$, $p < .001$, partial $\eta^2 = 0.20$) and time ($F_{(3, 99)} = 10.32$, $p = .002$, partial $\eta^2 = 0.097$) were discovered, but no significant group-by-time interaction was identified. The results suggested that both MCI groups had a higher FA rate compared with the two HO groups, and all groups increased their FA rate over time. Relative to their sex-matched controls, the F-MCI group had a higher item FA rate compared with the M-MCI group ($T_{(47)} = 2.11$, $p = .04$, Cohen's $d = 0.61$) in the immediate recall condition, but no difference between the two groups was detected in the delayed recall condition.

Together, for item memory, a female advantage was evident in HOs under the immediate recall condition, but absent in older adults with MCI when the analyses were based on absolute score comparisons. Furthermore, relative to their sex-matched controls, the F-MCI group exhibited worse item memory indicated by significantly lower item d', fewer hits, and more FAs compared to the M-MCI group under the immediate recall condition.

Table 3
Item and associative memory performance of the four groups.

	F–HO Mean (SD)	M-HO Mean (SD)	F-MCI Mean (SD)	M-MCI Mean (SD)	P value (two-tailed)
Item memory					
Total d'-immediate	3.61 (0.79)	3.07 (0.78)	2.53 (0.75)	2.92 (0.73)	$F_{(3,103)} = 9.86$, $p < .001$ [acd]
Total d'-delayed	3.41 (0.96)	3.13 (1.02)	2.07 (0.87)	2.13 (0.96)	$F_{(3,103)} = 13.70$, $p < .001$ [ab]
Hit rate-immediate	0.87 (0.17)	0.78 (0.18)	0.82 (0.11)	0.82 (0.16)	.21
Hit rate-delayed	0.86 (0.15)	0.79 (0.22)	0.75 (0.17)	0.74 (0.20)	.06
Total FA rate-immediate	0.01 (0.03)	0.02 (0.04)	0.11 (0.13)	0.06 (0.11)	$F_{(3,103)} = 8.37$, $p < .001$ [ade]
Total FA rate-delayed	0.03 (0.09)	0.02 (0.06)	0.15 (0.14)	0.13 (0.22)	$F_{(3,103)} = 6.04$, $p = .001$ [ab]
Associative memory					
Total d'-immediate	3.33 (1.24)	3.06 (1.23)	2.53 (1.00)	2.61 (1.50)	$F_{(3,103)} = 2.60$, $p = .05$ [a]
Total d'-delayed	3.13 (1.13)	1.97 (0.93)	1.55 (0.92)	1.86 (1.23)	$F_{(3,103)} = 12.75$, $p < .001$ [ac]
Hit rate-immediate	0.89 (0.11)	0.80 (0.24)	0.87 (0.15)	0.81 (0.20)	.22
Hit rate-delayed	0.86 (0.17)	0.71 (0.20)	0.76 (0.21)	0.79 (0.18)	$F_{(3,103)} = 3.00$, $p = .034$ [cf]
Total FA rate-immediate	0.10 (0.10)	0.10 (0.10)	0.27 (0.16)	0.18 (0.13)	$F_{(3,103)} = 10.79$, $p < .001$ [abe]
Total FA rate-delayed	0.13 (0.13)	0.14 (0.11)	0.33 (0.18)	0.28 (0.18)	$F_{(3,103)} = 11.62$, $p < .001$ [ab]

Associative memory

Significant main effects of group ($F_{(3, 99)} = 7.66$, $p < .001$, partial $\eta^2 = 0.19$) and time ($F_{(1, 99)} = 48.94$, $p < .001$, partial $\eta^2 = 0.33$) and a significant group-by-time interaction ($F_{(3, 99)} = 3.90$, $p = .011$, partial $\eta^2 = 0.11$) were discovered for associative d'. The post hoc

analyses revealed that under the immediate recall condition, the F-HO group outperformed both the F-MCI (p = .018, Cohen's d = 0.71) and M-MCI (p = .032, Cohen's d = 0.53) groups, whereas the M-HO, F-MCI, and M-MCI groups did not differ from one another. Under the delayed recall condition, the F-HO group outperformed the M-HO (p < .001, Cohen's d = 1.13), F-MCI (p < .001, Cohen's d = 1.08) and M-MCI (p < .001, Cohen's d = 0.76) groups, and the M-HO, F-MCI, and M-MCI groups did not differ from one another (Figure 1C).

The F-HO group exhibited significantly lower associative memory decay scores (difference between delayed and immediate recall) compared to the M-HO (p = .004, Cohen's d = 0.83) and F-MCI (p = .008, Cohen's d = 0.75) groups. The difference between the associative memory decay scores of the F-HO and M-MCI groups was marginally significant (p = .058, Cohen's d = 0.50), and the M-HO, F-MCI, and M-MCI groups did not have score differences. Compared to their sex-matched controls, although the two MCI groups had a comparable immediate recall performance , the F-MCI group exhibited significantly worse performance in delayed associative memory ($T_{(47)} = -4.06$, p < .001, Cohen's $d = -1.17$) compared with the M-MCI group (Figure 1D).

For the associative memory hit rate, a main effect of time was observed ($F_{(1, 99)} = 15.47$, p < .001, partial $\eta^2 = 0.14$), with a lower hit rate in the delayed recall condition than in the immediate recall condition; no main effect of group or group-by-time interaction was observed. Relative to their sex-matched controls, the F-MCI group had a lower hit rate for the delayed associative memory task than the M-MCI group in the delayed recall condition ($T_{(47)} = -3.26$, p = .002, Cohen's $d = -0.94$) but not in the immediate recall condition.

Regarding the total FA rate, a significant main effect of group ($F_{(3, 99)} = 11.83$, p < .001, partial $\eta^2 = 0.26$) and time ($F_{(1, 99)} = 43.60$, p < .001, partial $\eta^2 = 0.31$) and a significant group-by-time interaction ($F_{(3, 99)} = 26.20$, p = .014, partial $\eta^2 = 0.10$) were discovered. Follow-up analyses revealed that in both immediate and delayed recognition conditions, the two MCI groups had higher FA rates compared with the two HO groups (all p < .05); under the immediate recall condition, the F-MCI group also had a higher FA rate relative to the M-MCI group (p = .017, Cohen's d = 0.58). Furthermore, a faster increase in the number of FAs was observed over time in both the F-MCI (p = .036, Cohen's d = 0.52) and M-MCI (p = .003, Cohen's d = 0. 84) groups compared with in the F-HO group; the M-MCI group also exhibited a faster increase in the number of FAs over time compared with the M-HO group (p = .034, Cohen's d = 0.69). Relative to their sex-matched controls, the F-MCI group had a higher FA rate compared with the M-MCI group under the immediate recall condition ($T_{(47)} = 2.03$, p = .04, Cohen's d = 0.58), whereas the FAs between two MCI groups did not differ under the delayed recall condition.

To further determine whether associative memory was disproportionately impaired relative to item memory between groups, the immediate and delayed item *d'* were regressed out from associative *d'* under the immediate and delayed recall conditions, respectively. The results of a two-way ANOVA revealed a significant group-by-time interaction ($F_{(3, 99)} = 4.92$, p = .003, partial $\eta^2 = 0.13$), but no significant main effect of group or time was observed. The post hoc analyses revealed similar associative memory scores in all four groups when the item memory score was considered under the immediate recall condition. However, under the delayed recall condition, the F-HO group significantly outperformed the M-HO (p < .001, Cohen's d = 1.12) and F-MCI (p = .015, Cohen's d = 0.68) groups and marginally outperformed the M-MCI group (p

= .08, Cohen's d = 0.43) in associative memory when delayed item memory performance was controlled. The scores of the M-HO, F-MCI, and M-MCI groups did not differ from one another. A disproportionately greater associative memory decline (i.e., the difference between the delayed and immediate recall conditions) relative to item memory was observed in the M-HO ($p < .001$ Cohen's d = 1.01) and F-MCI (p = .023 Cohen's d = 0.64) groups compared with the F-HO group (Figure 1E).

Relative to their corresponding sex-matched controls, the F-MCI group had greater associative memory impairment even after item memory performance was controlled than did the M-MCI group in the delayed recall condition ($T_{(47)} = -3.72$, p = .001, Cohen's $d = -1.11$), but not in the immediate recall condition (Figure 1F).

In summary, for associative memory, a female advantage was evident in HOs but was not present in older adults with MCI based on absolute value comparisons. Specifically, the F-HO group outperformed the M-HO group by demonstrating less associative memory decay over 30 minutes, and the female advantage remained even when controlling for item memory performance. On the contrary, the two MCI groups performed similarly in the associative memory task, except that more FAs were made in the F-MCI group than in the M-MCI group under the immediate condition based on absolute value comparisons. Furthermore, relative to their controls of the same sex, the F-MCI group, but not the M-MCI group, exhibited a disproportionately greater associative memory decline relative to item memory.

Brain morphometric variations between groups

The raw data on the three medial temporal ROIs are presented in Table 2. The group analysis of these brain morphometric variables revealed a main effect of hippocampal volume ($F_{(3, 103)} = 3.09$, p = .015), but no group differences were observed for the cortical thickness of parahippocampal regions or PRC/EC regions. The F-HO group exhibited a greater hippocampal volume than the F-MCI (p = .047, Cohen's d = 0.51) and M-MCI (p = .043, Cohen's d = 0.66) groups. Similarly, the M-HO group had a greater hippocampal volume than the F-MCI (p = .01, Cohen's d = 0.78) and M-MCI (p = .01, Cohen's d = 1.02) groups, whereas no sex differences in hippocampal volume were observed within the MCI and HO cohorts.

Relative to their sex-matched controls, the F-MCI group exhibited a greater decrease in cortical gray matter thickness in the PRC/EC regions compared with the M-MCI group ($T_{(47)} = -2.12$, p = .04, Cohen's d = 0. 65), but no difference in hippocampal volume or parahippocampal thickness was detected between the two MCI groups (Figure 2A).

In summary, the two MCI groups were characterized by significant hippocampal atrophy compared to the two HO groups, supporting the validity of our group classification based on neuropsychological measures. Furthermore, the two MCI groups were comparable in volume or cortical thickness across the three medial temporal ROIs (i.e., the hippocampus, parahippocampus, and PRC/EC regions) when the analyses were based on absolute value comparisons. Compared to their sex-matched controls, however, the F-MCI group revealed more atrophy in PRC/EC regions than that in the M-MCI group, suggesting that the F-MCI group may be in a more advanced stage of the disease continuum compared with the M-MCI groups by the time they were diagnosed with MCI according to conventional standards.

Associations between memory test performance and hippocampal volume

We computed Pearson's correlations between memory performance (i.e., item and associative memory *d'* variables) with the standardized residual values (controlling for age for all variables, and additionally controlling for head size for the hippocampal volumetric variable) related to the three ROIs. For the entire study group, the results revealed that larger hippocampal volumes were significantly associated with better performance in delayed item memory (r = .37, p < .001) and delayed associative memory (immediate: r = .28, p = .004) tests. A marginal association of hippocampal volume with immediate item memory (r = .22, p = .018) and immediate associative memory (r = .19, p = .038) was also observed. No significant associations between parahippocampal thickness and memory variables were observed. Furthermore, greater cortical thickness in the PRC/EC regions was positively correlated with performance in item memory (immediate: r = .31, p = .002; delayed: r = .27, p = .005) and immediate associative memory (r = .37, p < .001) tests.

When the analysis was restricted to female participants across the HO and MCI groups, significant associations were revealed between hippocampal volume and delayed item memory (r = .42, p = .001) as well as between hippocampal volume and delayed associative memory (r = .42, p = .001). Greater cortical thickness in the parahippocampal regions was marginally associated with delayed item memory performance (r = .25, p = .04). Greater cortical thickness in the PRC/EC regions was significantly correlated with delayed associative memory test performance (r = .33, p = .01) and marginally correlated with item memory test performance (immediate: r = .29, p = .018; delayed: r = .31, p = .015) and immediate associative memory test performance (r = .25, p = .036; Figure 2B). When the analysis was restricted to male participants across the HO and MCI groups, no significant brain–memory association was found, and only a marginally significant association between hippocampal volume and delayed item memory test performance was observed (r = .31, p = .03).

In summary, we found significant correlations between medial temporal structures, especially the hippocampus and PRC/EC regions, and item memory, as well as associative memory. However, the brain structure–behavior associations were particularly relevant for delayed recall conditions and were driven primarily by the older women sample rather than the older men sample.

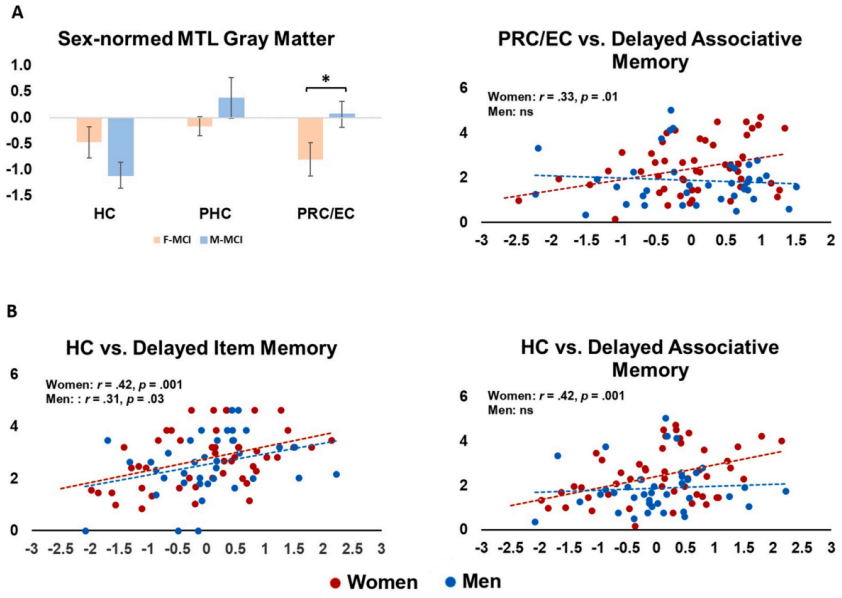

Fig. 2 (A) Medial temporal lobe (MTL) gray matter morphometry for the regions of interest [volumetric measures for the hippocampus (HC); cortical thickness measures for the parahippocampus (PHC) and perirhinal/entorhinal (PRC/EC) thickness] for women and men with mild cognitive impairment (MCI) indicated by *z*-scores relative to their sex-matched controls. Bilateral hippocampal volumes were corrected for differences in head size by regressing out the estimated total cranial vault volume. Error bars denote standard errors of the mean. F-MCI = female with MCI; M-MCI = male with MCI.*p < .05. (B) Three correlation plots between delayed item and associative memory discriminability (*d'*) with MTL structures for the full female (red) and male (blue color) samples. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Discussion

The present study investigated sex differences in item and associative memory of older adults with and without aMCI. The association between item and associative memory task performance and medial temporal morphometric variations were also examined. Through conjointly examining item and associative memory scores for the same task, the present study revealed several novel findings. First, in HOs, a female advantage was observed for both item and associative memory. The female advantage was salient for item memory under the immediate recall condition and associative memory under the delayed recall condition, even when item memory performance was controlled. Second, in the aMCI cohort, the female advantage was absent for both item and associative memory; women with aMCI performed similarly to men with aMCI in the associative memory task, with the exception of more FAs observed in women with aMCI relative to men with aMCI. Relative to their sex-matched controls, however, women with aMCI had greater impairment than men with aMCI on both item and associative memory, and this associative memory impairment persisted even after item memory performance was controlled. Third, although the two MCI groups were comparable in terms of medial temporal regional measures, relative to their sex-matched controls, women with aMCI had greater atrophy in the PRC/EC regions compared with men with aMCI. Fourth, the measurements (volumes or thickness) of both the hippocampus and PRC/EC regions were associated with item and associative memory, but the brain–behavioral association was significant only for female participants.

In support of our hypothesis, a female advantage was observed for both item and associative memory in HOs. Our findings are consistent with studies demonstrating better item memory [2, 8, 9, 12-17] and associative memory [11, 15-17] in women, and a verbal memory reserve advantage for women with advanced age was indicated after we accounted for baseline cognitive status, age, education level, vascular burden, and ApoE e4 carrier status. Notably, the female item memory advantage was evident only in the immediate recall condition, not in the delayed recall condition. By contrast, the female advantage in associative memory was evident only for the delayed recall condition, even after controlling for item memory. Because no studies have jointly compared item and associative memory for both immediate and delayed recall conditions, it was difficult to compare our findings directly with those of other studies. Several studies have attributed the female advantage in verbal memory to women having greater spontaneity than men in using encoding strategies, particularly semantic or phonological strategies, for verbal materials [9, 48-50]. Although the employment of encoding strategies may account for our findings on item memory under the immediate recall condition, such strategies did not appear to account for female advantages in associative memory identified in the present study because the female associative memory benefit was only observed in the delayed recall condition, not the immediate recall condition. Moreover, the female advantage in verbal memory has been linked to advantages in verbal ability [51]; however, this factor did not appear to account for our results because the F-HO and M-HO groups did not have different scores in standardized neuropsychological tests assessing verbal abilities, namely the Category Fluency Test and Boston Naming Test. Furthermore, these findings cannot be directly linked to macrostructural differences in medial temporal gray matter regions because the two HO groups were comparable in volumes or thickness across the three medial temporal ROIs (i.e., hippocampus, parahippocampus, and PRC/EC regions).

Although the mechanisms of the effects of sex on item and associative memory remain unclear, our results suggest that sex is an important factor in cognitive aging. In the present study, we found that older

men, but not older women, had greater decay in associative memory compared with item memory after a 30-min delay, which may put older men at a heightened risk of developing MCI. Studies have reported that men were more likely to develop MCI (both aMCI and nonamnestic subtypes) than women [52, 53], although conflicting reports exist, likely due to methodological differences among the studies [54]. Overall, our study extended findings from previous studies and revealed that the female advantage was particularly remarkable in item learning and associative information retention in older adults without MCI.

In the aMCI cohort, in support of our hypothesis, the female advantage was not present in the associative memory task. In fact, women with aMCI relative to men with aMCI had more FAs for the associative memory task. Moreover, through a comparison with sex-matched healthy controls, we found that women with aMCI had fewer hits, more FAs, and worse overall immediate item memory and delayed associative memory than men with aMCI. Additionally, the decline in associative memory over time in women with aMCI was greater than that in men with aMCI, even after item memory performance was controlled.

Although the present study was the first to report such results, our findings of a larger performance gap between cognitively healthy women and those with aMCI compared with cognitively healthy men and those with aMCI men accord with findings from the literature concerning item memory or story memory in populations with aMCI [8, 55] or AD [6, 56, 57]. The findings also suggest that the female aMCI group had greater cognitive decline in verbal memory than the male aMCI group by the time they were diagnosed as having aMCI by conventional standards; this finding was consistent with those of other studies [8, 55]. Notably, the female disadvantage was not evident when the analyses were based on absolute score comparisons between the female and male MCI groups. Similarly, the two aMCI groups performed equivalently on the MMSE and standardized neuropsychological tests, including those assessing language and episodic memory abilities, and were also similar in age, education level, vascular burden, and apolipoprotein status. Taken together, these findings suggest that when a fixed threshold is used without considering sex differences for defining impairment, a true diagnosis of aMCI may be delayed in women because the female advantage in verbal memory may mask underlying neurodegeneration, particularly in the earlier disease stages. In contrast to our findings, some studies have reported a female advantage in word list tests in aMCI cohorts [2, 14] or indicated no sex effect in associative memory tests in MCI cohorts relative to their sex-matched healthy controls [19 2, 14, 194, 16, 21](Beinhoff, et al., 2008; Murphy, et al., 2020; Sundermann, et al., 2016)(Beinhoff U *et al.* 2008; Sundermann EE *et al.* 2016; Murphy KJ *et al.* 2020). Some potential explanations for the discrepancy between our findings from those in these aforementioned studies are that these studies had either a small sample size (i.e., six women and nine men with MCI)[19], did not control for education levels between the two sex groups [2], or did not control for clinical variables [2, 14, 19]. For example, several studies have indicated a higher prevalence of cerebrovascular burden in older men than in older women, which may partially account for female advantages in cognition [58, 59].

In line with our behavioral findings, a similar pattern was also observed in the brain-related variables; men and women with aMCI appeared to be comparable in volumes or cortical thickness across the three medial temporal ROIs when the two sex groups were compared. Relative to their sex-matched healthy controls, however, the F-MCI group had greater atrophy in PRC/EC regions than the M-MCI group, indicating that the F-MCI group may be in a more advanced stage of the disease continuum compared with

the M-MCI group. Our findings on CDR sum of boxes scores also support this argument; relative to their sex-matched healthy controls, the F-MCI group exhibited greater functional impairment based on the CDR index compared with the M-MCI group.

Overall, our findings related to MCI cohorts echo those of other studies suggesting that cognitive reserve in verbal memory better allows women to mask their verbal memory impairment and brain pathology until a later disease state [8, 60-62]. Consequently, males may be diagnosed with aMCI at a younger age than females. Once a diagnosis has been made, however, women with aMCI may have greater functional decline compared with men with aMCI. In the present study, because our aMCI sample might have comprised individuals with milder cognitive impairment compared with those in prior studies due to the operational definition of objective cognitive impairment for MCI (i.e., −1 SD rather than −1.5 SD lower than the norms) used, we provide further evidence that the masking effect for cognition and brain pathology could be detected in the early stages of prodromal dementia through proper assessment.

In the brain structure–behavior associations, we found that the integrity of the hippocampus and PRC/EC regions was positively associated with memory performance, especially with the delayed associative memory score, of older women but not older men. Medial temporal structures, especially the hippocampus, are believed to play a key role in associative memory by supporting the binding and recollection of novel relational associations [63-65], and a positive correlation between medial temporal structural measures and memory performances for older women suggests that greater gray matter volumes or cortical thickness of the medial temporal structures improves memory performance when binding items are required during novel associative memory encoding and retrieval.

Although the underlying mechanisms to account for the absence of a significant association between medial temporal structures and memory performance in older men remains unclear, such findings are consistent with those of related studies [18, 66]. A possible explanation for older men not exhibiting significant brain–memory correlations may be that their novel associative memory relied more on strategic processes, which are less medial temporal dependent, than on binding or recollection processes, given that both associative and strategic components may contribute to associative memory performance in older adults [67, 68]. In our associative memory task, verbal materials were presented visually. Although the stimuli were considered verbal materials containing unique phonological and semantic information, processing the visual graphemes of these Chinese characters may require visuospatial strategies or visuospatial working memory processing [69], which are associated with a male advantage [51, 70], and such processing may rely on structures outside of the medial temporal regions [67, 71, 72]. Future studies are required to investigate the underlying mechanisms of sex differences in strategic versus recollection processes for associative memory as well as their relationship with the broader brain network.

Some limitations of our study should be noted. First, although the findings remain controversial, studies have indicated that undergoing menopause hormone therapy may have negative cognitive effects on postmenopausal women, particularly women with low cognitive function at baseline [73-75]. Because we did not obtain information on hormone therapy on female participants, particularly those with MCI, the potential confounding effects of this therapy on our results cannot be ruled out.

Second, because the large number of homophones in the Chinese language makes the lexical mapping impossible without further context or written information, we presented all stimuli visually instead of in

audio-mode. Although the use of visually presented verbal stimuli in other similar, English language–based studies is not uncommon (e.g., [17]), the logographic characteristics of the Chinese language may have confounded our sex-specific findings due to participants potentially using a mixture of visual memory and verbal memory. Nevertheless, we observed a robust female advantage in item and associative memory among HOs, which was consistent with studies in which tests were conducted verbally in English [9], indicating that our task manipulation was valid. Future studies could further assess whether the female advantage observed in HOs and the female disadvantage observed in women with MCI relative to their counterparts may be even more pronounced when audio-based verbal stimuli are used instead of visual-based verbal stimuli. Third, we did not consider biomarkers such as amyloid beta burden in our sample, which may account for some of our behavioral results; some studies have reported that greater cortical amyloid beta burden was related to poorer immediate item memory performance in both men and women with MCI [60, 76]. Fourth, this study's cross-sectional design limited our ability to determine the temporal or causal relationship between associative memory and medial temporal structures as well as to directly evaluate the sex-specific effect associated with cognitive reserve theory [7]. Population-based longitudinal analyses could offer a more definitive evaluation of the hypothesis that the female advantage in verbal memory may serve as a form of cognitive reserve.

Conclusion

The present study revealed that the female advantage in both item and associative memory was evident in HOs, and this advantage was particularly salient for delayed associative memory performance even when item memory performance was controlled. By contrast, despite the comparable gray matter in medial temporal structures when women and men with aMCI were compared, we found that women with MCI may be in a more advanced stage of the disease continuum because women with aMCI, relative to men with aMCI, exhibited greater impairments in the associative memory task relative to healthy control baseline, greater atrophy in PRC/EC regions, and poorer global cognitive function based on sex-matched norms. These findings support the hypothesis that cognitive reserve accounts for the female advantage in verbal memory; this advantage observed in normal aging appears to continue into the early prodromal stage of dementia and delay the detection of MCI in women. Future longitudinal studies are required to confirm this hypothesis. The different brain structure–memory associations in women and men may also indicate different mechanisms in completing associative memory tasks. Further investigations of sex effects on prodromal AD could elucidate dementia risk assessment that improve diagnostic accuracy at early disease stages as well as increase the accuracy of outcome evaluations when interventions have been provided.

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國科會補助專題研究計畫出席國際學術會議心得報告

日期：2023年9月30日

計畫編號	MOST 109-2629-H-002-001-MY3		
計畫名稱	性別差異於認知老化與阿茲海默症早期偵測之研究		
出國人員 姓名	張玉玲	服務機構 及職稱	國立臺灣大學心理學系暨研究所/教授
會議時間	2023年 9月 28日 至 2023年 9月30 日	會議地點	日本筑波大學
會議名稱	(中文) (英文) University of Tsukuba-National Taiwan University Joint Symposium on Digital Health and Medicine 2023		
發表題目	(中文) (英文) Enhancing Dementia Detection and Cognitive Well-Being in Older Adults Through Human-Robot Interaction		

一、參加會議經過

此行最主要的目的為參加 University of Tsukuba-National Taiwan University Joint Symposium on Digital Health and Medicine 2023 並在大會上給予專題演講 "Enhancing Dementia Detection and Cognitive Well-Being in Older Adults Through Human-Robot Interaction"，也藉此機會與筑波大學 AI 中心的幾位教授共同討論未來合作的方向，並擬定工作計畫。這次研討會的主題為 Digital health and medicine，主要因應全球人工智慧技術在各領域的廣泛應用性，筑波大學在醫學領域在日本一直佔有重要地位，而近年來成立亦 AI 中心，此與臺灣大學近年來的發展方向一致，因此透過兩方校務代表協商，因而訂定參訪與會議議程。

二、與會心得

能夠與日本眾多知名學者分享本人的研究成果，且共同探討可以合作的研究議題，並擬定具體工作計畫，是相當難得的經驗。在過程中體會到日本學者處理研究資料細緻的一面，也體會到臺灣在研究資源上的彈性與豐富，雙邊的合作建立在互補與共同目標上，因此討論過程相當愉快也很有效率。不過因為整體行程非常緊湊，並無多餘時間探索筑波當地的風土人情，較為可惜。

三、發表論文議程

請見附件

四、攜回資料名稱及內容

研討會之議程集與本會各個口頭與壁報的摘要資料。

University of Tsukuba - National Taiwan University
Joint Symposium on Digital Health and Medicine 2023

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September 29th 2023 (Admission Free)

Room 110, Laboratory of Advanced Research A, University of Tsukuba
1-1-1 Tennodai, Tsukuba, Ibaraki 305-8577 Japan

Time (JP)	Subject	Speaker/Affiliation	Moderator
Morning Session			
08:30 - 09:00		Reception	
09:00 - 09:10	**Opening Remark**	• **Prof. Jun Ikeda**, Vice President and Executive Director for Global Affairs of UT • **Prof. Hsiao-Wei Yuan**, Vice President for International Affairs of NTU	
09:10 - 09:15		Group Photo	
09:15 - 09:55	**Fostering Well-Being through Collaboration of Medicine and AI**	**Tetsuya Sakurai** Director, C-AIR Professor, Institute of Systems and Information Engineering, UT	**Prof. Li-Chen Fu**
09:55 - 10:35	**The Roadmap of Telehealth in the Future**	**Yi-Lwun Ho** Associate Dean, College of Medicine, NTU Director, Internal Medicine, NTUH Director, Telehealth Center, NTUH	
10:35 - 11:00		Coffee Break & Poster Session	
11:00 - 11:25	**Privacy-preserving data collaboration analysis for multiple medical institutions**	**Akira Imakura** Associate Professor, Institute of Systems and Information Engineering, UT	**Prof. Hiroyuki Nishiyama**
11:25 - 11:50	**Transforming Big Data to Better Healthcare Through a Medical Data Analytics Framework**	**Weichung Wang** Professor, MeDA Lab and Institute of Applied Mathematical Sciences, NTU	
11:50 - 13:20		Lunch Break & Poster Session	
Afternoon Session			
13:20 - 13:30		Reception	
13:30 - 13:55	**Spectral methods for dimensionality reduction, clustering, and network embedding in biological data analysis**	**Yasunori Futamura** Associate Professor, Institute of Systems and Information Engineering, UT	**Prof. Weichung Wang**
13:55 - 14:20	**Biomedical Applications of Machine Learning & AI for Drug Design and Biosensors**	**Chii-Wann Lin** Professor, Biomedical Engineering, NTU	
14:20 - 14:35	**Glioblastoma Prognosis Classification: Integrating Clinical Experience with Artificial Intelligence**	**Hsiang-Kuang Tony Liang** Director, Division of Proton Therapy Center, NTU Cancer Center; Assistant Professor, Biomedical Engineering, NTU	**Prof. Takahito Nakajima**
14:35 - 14:50	**AI in radiotherapy: Real-time lung tumor tracking with X-ray images**	**Toshiyuki Terunuma** Research Associate, Proton Medical Research Center, UT	
14:50 - 15:15	**Empirical Myoelectric Feature Extraction and Pattern Recognition in Hemiplegic Distal Movement Decoding**	**Alexander Zaboronok** Assistant Professor, Department of Neurosurgery, Institute of Medicine, UT	
15:15 - 15:40		Coffee Break & Poster Session	
15:40 - 16:05	**Depression Detection and Emotional Support with Social Assistant Robot**	**Li-Chen Fu** Director, AIROBO Chair Professor, NTU	**Prof. Tetsuya Sakurai**
16:05 - 16:30	**Enhancing Dementia Detection and Cognitive Well-Being in Older Adults Through Human-Robot Interaction**	**Yu-Ling Chang** Professor, Department of Psychology; Director, Imaging Center for Integrated Body, Mind, and Cultural Research	
16:30 - 16:55	**Psychiatric neuroimaging using with diffusional MRI**	**Miho Ohta** Professor, Department of Psychiatry, Institute of Medicine, UT	**Prof. Chii-Wann Lin**
16:55 - 17:20	**Using AI for Liver Disease Management**	**Tung-Hung Su** Clinical Associate Professor, Dept. Internal Medicine, NTU	
17:20 - 17:25	**Closing Remarks**	**Prof. Li-Chen Fu** **Prof. Tetsuya Sakurai**	

筑波大学 University of Tsukuba　國立臺灣大學 National Taiwan University　AIROBO　MAHC Medical and Health Care　CAIR Center for Artificial Intelligence Research　TB Tsukuba Digital-Bio International Center

109年度專題研究計畫成果彙整表

計畫主持人：張玉玲			**計畫編號：**109-2629-H-002-001-MY3		
計畫名稱：性別差異於認知老化與阿茲海默症早期偵測之研究（L03）					
成果項目			量化	單位	質化 （說明：各成果項目請附佐證資料或細項說明，如期刊名稱、年份、卷期、起訖頁數、證號...等）
國內	學術性論文	期刊論文	0	篇	
		研討會論文	0		
		專書	0	本	
		專書論文	0	章	
		技術報告	0	篇	
		其他	0	篇	
國外	學術性論文	期刊論文	7	篇	1.Lai, Y.M. & Chang*, Y.L. (2023). Age-related differences in associative memory recognition of Chinese characters and hippocampal subfield volumes. Biological Psychology. 183:108657. doi: 10.1016/j.biopsycho.2023.108657. 2.Lin, Y.R., Chi, C.H.& Chang*,Y.L. (2023). Differential decay of gist and detail memory in older adults with amnestic mild cognitive impairment. Cortex. doi.org/10.1016/j.cortex.2023.04.002. 3.Chang*,Y.L & Moscovitch, M. (2022). Sex differences in item and associative memory among older adults with amnestic mild cognitive impairment. Neuropsychologia. 5;176:108375. doi: 10.1016/j.neuropsychologia.2022.108375. 4.Chi, C.H., Yang, F.C., & Chang*, Y.L. (2022). Age-related volumetric alterations in hippocampal subiculum region are associated with reduced retention of the “when” memory component. Brain and Cognition. https://doi.org/10.1016/j.bandc.2022.105877. 5.Chang*, Y.L., Luo, D.H., Huang, T.R., Yeh, S.L., Goh, J.O.S., & Fu, L.C (2022). Identifying Mild Cognitive Impairment by Using

					Human–Robot Interactions. Journal of Alzheimer’s Disease. 85(3):1129-1142 doi: 10.3233/JAD-215015. 6.Chang*, Y.L., Zhuo, Y.Y.,& Luo, D.H. (2021). Education moderates the negative effect of apolipoprotein E epsilon 4 on response inhibition in older adults. Journal of Alzheimer’s Disease 82(3):1147-1157. 7.Chang*, Y.L., Chao, R.Y., Hsu, Y.C., Chen, T.F., & Tseng, W.Y. (2021). White matter network disruption and cognitive correlates underlying impaired memory awareness in mild cognitive impairment. NeuroImage: Clinical, 30:102626. doi: 10.1016/j.nicl.2021.102626
		研討會論文	24		1.Nguyen, T.T. & Chang, Y.L. (2024) Convergent Patterns of Cognitive Heterogeneity in Prodromal Stages of Dementia with Data-Driven Machine Learning. The 2024 International Neuropsychological Society Annual Meeting. 2.Yang, H.Y., Shun, Shiow-Ching, & Chang, Y.L.(2024). Adjustment process of cognitive impairment in individuals with colorectal cancer: a qualitative study. 35th International Nursing Research Congress. 3.Chang*, Y.L. (2023).Integration of neuropsychology and ai for optimizing early dementia detection and cognitive well-being. University of Tsukuba, Invited talk. 4.Nguyen, T., Tsai, M.S., Wang, j.R., Chiu, Y.L., Lee, C.Y. & Chang*, Y.L. (2023). Cognitive heterogeneity in prodromal dementia with data-driven machine learning. University of Tsukuba. 5.Chang*, Y.L. (2023). Early detection of dementia & cognitive intervention using artificial intelligence for older adults. University of Tsukuba, Invited talk.

					6.Chang*, Y.L. (2023). Enhancing Early Detection of dementia through Synergistic Collaboration between Neuropsychology and AI Techniques. The 2023 International Neuropsychological Society mi-year Annual Meeting. 7.Chang*, Y.L. & Wang, M.Y. (2023). The influence of social information and self-referencing on associative memory: an examination of age-related interaction effects. The 2023 International Neuropsychological Society mi-year Annual Meeting. 8.Cheng. W.Y.& Chang, Y.L. (2023). Enhancing Collaboration in the Neuropsychology of Taiwanese: Clinical and Theoretical Considerations. The 2023 International Neuropsychological Society mi-year Annual Meeting. 9.Lai, Y.M. & Chang, Y.L.(2023). Age-related differences in hippocampal subfield volumes are linked to associative memory recognition. The 2023 International Neuropsychological Society mi-year Annual Meeting. 10.Li, K.A., Chien, S.E., Chang, C. Y., Chang, Y.L., Chen, T.F., Yeh, S.L., & Chien, S.Y. (2023) Eye tracking-based cognitive performances in MCI seniors and healthy controls. The 2023 International Neuropsychological Society mi-year Annual Meeting. 11.Lin, Y.R., Chi, C.H., & Chang*, Y.L. (2023). Distinct patterns of gist and detail memory decay in older adults with amnestic mild cognitive impairment. The 2023 International Neuropsychological Society mi-year Annual Meeting. 12.Lai, Y.M., Chiu, Y.L., Wang, J.R., Tsai, M.S., Lee, C.Y., & Chang*, Y.L. (2023). Retrospective time perception deficits in older adults with amnestic mild cognitive Impairment. The 2023 International Neuropsychological Society mi-year Annual Meeting.

					13.Chi, C,H., Lin, Y.R., & Chang*, Y.L. (2023).Significant decay continuously in the when component is differently associated with specific hippocampal subfield volumes in individuals with amnesic mild cognitive impairment. The 2023 International Neuropsychological Society mi-year Annual Meeting. 14.Tang, P.F., Liu, C.H., Chen, S.Y., Goh, J., Chang, Y.L. (2023). Relationships of changes in blood pressure and cardiorespiratory fitness with changes in the brain after light-to-moderate exercises in middle-aged and older adults with cardiovascular risk factors. The 29th Annual Meeting of the Japanese Association of Cardiac Rehabilitation. 15.Yang, C.C., Yeh, S.L., Chien, S. E., Chen, Y.C., Huang,T. R., Chang, Y.L., Goh, J., & Fu, L.C. (2023). The effect of face-to-face interaction on older adults' attitudes toward robots in human-computer interaction. The 25th International Conference on Human-computer Interaction Annual Meeting. 16.Chi, C,H. & Chang, Y.L. (2022). Expanding retrieval practice boost episodic memory in individuals with amnestic mild cognitive impairment. The 2022 International Neuropsychological Society Annual Meeting. 17. Li, K.A., Chien, S.E., Chang, C.Y., Chang, Y.L., Chen, T.F., Yeh, S.L., & Chien, S.Y. (2022).Development of automatic eye tracking-based cognitive assessment battery. Asia Pacific Regional Conference of Alzheimer's Disease International. 18.Lin, S.Y., Chang, H.L., Wai, T., Fu, L.C.
		專書	0	本	
		專書論文	0	章	
		技術報告	0	篇	
		其他	0	篇	

參與計畫人力	本國籍	大專生	6	人次	6名大學部學生透過暑期短期研究計畫的參與，至研究室學習個案收案與資料分析等研究流程，並將成果於校內做報告告。
		碩士生	7		7名碩士班研究生以及一名碩士級專任助理在篩檢高齡受試者，資料收集，以及分析資料與閱讀文獻上透過做中學，不僅在專業能力上有所增長，也協助計畫往前推動。
		博士生	1		本計畫執行期間，一位博士生參與計畫執行，其中一位於2023/07榮獲國際神經心理學年會最佳記憶研究之獎項，並順利將研究成果發表於國際期刊。
		博士級研究人員	1		透過本計畫，延攬一位博士級博士後研究員，協助參與計畫，同時亦順利取得東吳大學助理教授職位。
		專任人員	0		
	非本國籍	大專生	0		
		碩士生	1		本計畫執行過程培育了一名來自馬來西亞的華僑心理學研究所碩士生。
		博士生	1		透過本計畫培育一名越南籍的博士生(中研院TIGP-INS學程)，該生目前為二年級，已著手撰寫研究成果，近期內將投稿國際期刊。
		博士級研究人員	0		
		專任人員	0		
其他成果 （無法以量化表達之成果如辦理學術活動、獲得獎項、重要國際合作、研究成果國際影響力及其他協助產業技術發展之具體效益事項等，請以文字敘述填列。）			計畫主持人去年度擔任台灣國際神經心理學會的主辦方籌備人員，透過超過百位的國際學者參與，成功促進台灣與世界神經心理學的交流。計畫主持人亦於2023年底當選亞洲神經心理學學會之國際理事，任期兩年，此對於促進台灣神經心理學的國際地位，具有重要影響。計畫主持人亦與日本筑波大學與美國多所大學(哈佛大學，哥倫比亞大學，布蘭蒂大學)的學者建立研究合作計畫，目前有多項計畫與研究成果準備發表中。此外，計畫主持人於2023年接任中華心理學刊(心理學一級期刊)偕同主編，同時亦擔任台灣心理學會理事，在諸多先進的帶領下，一同為國內心理學界貢獻一份心力。		