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Characteristics of Associative Memory Deficits in Amnestic Mild Cognitive Impairment*

WANG Peng-Yun[1,2], LI Juan[1)**], LI Hui-Jie[1)], LI Bing[1,2], LI Xin[1,2], ZHOU Ting[1,2]
([1)] *Center on Aging Psychology, Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing* 100101, China;
[2)] *University of Chinese Academy of Sciences, Beijing* 100049, China)

Abstract Amnestic mild cognitive impairment (aMCI) patients show impairment in both item and associative memory. The current study administered the widely used associative and item memory tests from the Clinical Memory Scale to investigate whether aMCI patients are more impaired in associative memory than item memory. In addition, we aimed to analyze an associative memory test (the paired-associate learning test) in order to investigate in detail the nature of associative memory impairment in aMCI patients. Twenty-five individuals with aMCI and 28 healthy controls took part in the study. Two associative memory tests (paired-associate learning test and associative recall), two item memory tests (free recall of pictures and recognition of meaningless figures), and a set of neurocognitive tests were administered to the participants. aMCI patients performed significantly worse than healthy older adults in both associative memory tests, even when controlling for impairment in the item memory tests. In addition, ROC curve analysis indicated that discriminative power was higher in associative than in item memory tests. Further, the results of the paired-associate learning test indicated that, compared to normal older adults, aMCI patients showed more deficits in remembering the easy word pairs, relative to the difficult word pairs. Our results confirm that aMCI patients demonstrate greater deficits in associative memory than in item memory. In addition to the impairment in creating memory links between items, aMCI patients may have deficits in using the semantic information presented by the items. The associative memory tests showed higher discriminative power than item memory tests in the identification of aMCI patients. Including associative memory testing in future neurocognitive assessment protocols could be helpful to improve the "hit rate" of aMCI detection.

Key words amnestic mild cognitive impairment, associative memory, item memory
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Individuals with mild cognitive impairment (MCI) are at high risk for progression to Alzheimer's disease (AD) or other types of dementia (annual conversion rate of approximately 10% to 15%) compared to healthy controls (conversion rate of approximately 1% to 2%)[1–2]. Amnestic mild cognitive impairment (aMCI) is defined as a transitional condition to AD characterized by episodic memory deficits and intact functional abilities[3].

Episodic memory, associated with the ability to learn and retain new information and the most-developed and late-grown memory system, is especially vulnerable to normal aging [4]. Previous studies have found that episodic memory deficit is one of the core deficits in aMCI[5–6]. Episodic memory has also been found to play an important role in predicting the transition from aMCI to AD. Other researchers found that individuals with episodic memory deficits had more than twice the risk of developing AD than those with other cognitive deficits, and that lower episodic memory performance was associated with an increased risk of AD over a 10-year follow-up period [7].

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**Corresponding author.
Tel: 86-10-64861622, E-mail: lijuan@psych.ac.cn
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Among the various tasks developed to explore episodic memory deficits in aMCI patients, free recall and recognition tests assessing item memory are the most commonly used. Recently, however, several studies have shown that associative memory is selectively impaired in aMCI, affecting tasks such as word-pairs, visual-spatial association, font color and item association, cues-item association, and face-place association, among others[8–11]. Evidence has also been presented suggesting that associative memory tests might be sensitive enough to distinguish MCI with a high probability of conversion to AD [10]. Item and associative memory involve different memory content. Item memory is the process of remembering individual items (such as words or objects) independent of any other information associated with them at acquisition, while associative memory involves remembering relationships among items of information, such as remembering words that were paired together and remembering objects and their locations [12]. To our knowledge, only two studies have compared the difference in impairment between item and associative memory in aMCI patients[12–13]. Using a cue-item recall test, an object-location recall test, and a symbol-symbol recall test, researchers found that associative memory was more seriously impaired than item memory in aMCI patients. However, the materials of the associative memory tests used in these studies were visual; their conclusions should be verified further using other materials such as auditory stimuli. Moreover, most of the evidence about item and associative memory deficit in individuals with aMCI was collected from Caucasian samples; until now, only one study has explored item memory deficits in Chinese participants [14]. According to China's Sixth Population Census, as of the end of 2010, the population of China included 177.65 million people age 60 and over (13.62% of total population), and 118.83 million aged 65 and over (8.87% of the overall population) [15]. Therefore, considering the potential cross-cultural applicability, it is very important to identify a sensitive tool to detect aMCI in Chinese older adults as soon as possible.

The Clinical Memory Scale (CMS) [16–17] is a widely used standardized tool designed by researchers studying the psychology of aging at the Institute of Psychology, Chinese Academy of Sciences. Of the top 10 instruments most used to measure psychological health in China between 1979 and 2007, this is the only one natively designed for Chinese patients[18]. The CMS consists of five memory subtests: the paired-associate learning and associative recall tests of associative memory, and the free recall of pictures and recognition of meaningless figures for item memory; the fifth is a test of directed memory. In the present study, we used native item and associative memory tests with auditory stimuli to further examine associative memory deficits in a sample of Chinese aMCI patients and explore whether associative memory was more impaired than item memory.

In addition, using receiver operating characteristic (ROC) curve analysis, we aimed to further test whether associative memory tests have better discriminative power in identifying aMCI patients than item memory tests. The ROC graph plots all of the sensitivity/specificity pairs that result from continuously varying the decision threshold over the entire range of results observed. Sensitivity, or the true positive rate, is shown on the y-axis [defined as (number of true positive test results) / (number of true positive + number of false negative test results)]; the false positive rate, or 1 – specificity, is plotted on the x-axis [defined as (number of false-positive results) / (number of true-negative + number of false-positive results)]. The area under a ROC curve (AUC, region from 0.5 to 1) can provide the global measurement index of diagnostic accuracy in clinical medicine. The larger the AUC is for a test, the higher its overall diagnostic accuracy is. AUC can be calculated using software such as Statistical Product and Service Solutions (SPSS).

Given that the word pairs used in the paired-associate learning test include both easy (existing semantic relationship between the words in each pair) and difficult pairs (in which the words are not related at all), we also wanted to investigate the memory deficit of aMCI patients with these two difficulty levels. We expected that the group difference would be larger for the difficult word pairs than the easy word pairs, because aMCI patients have more serious impairment in the ability to actively use strategies to create memory links between the item pairs than in using the semantic relationship between the items.

1 Methods

1.1 Participants

Individuals with aMCI were recruited from the community (n = 17) and by physician referral (n = 8). Diagnoses of aMCI were made according to published criteria[2–3]:

(1) The presence of subjective complaints from the participant or informant.

(2) Objective memory impairment as measured by logical memory items selected from the Wechsler Memory Scale-Revised, Chinese version [19], and directed memory selected from the CMS. We used the more liberal criterion of 1 SD below the norm of one or two memory tests for the cut-off scores, as a previous study suggested that the traditional 1.5 SD cut-off would reduce the possibility of detecting early stage memory impairment[20].

(3) Preserved activities of daily living (ADL, ≤ 18 points), measured by the ADL questionnaire[21].

(4) Normal general cognitive function, measured by Mini-Mental State Examination (MMSE) [22]. The cut-off score for the MMSE is 24 points for those with middle school or higher education, 20 points for individuals who completed primary education, and 17 points for uneducated older adults[22].

(5) Depression score as measured by the Center for Epidemiological Studies Depression Scale (CES-D) lower than 16 points[23].

Healthy controls were recruited from the same population. They were defined by scoring in the normal range on the two objective memory tests, ADL (≤ 18 points), MMSE, and CES-D (< 16 points), and no complaints of memory problems.

Participants were excluded in cases of (1) a history of head trauma resulting in loss of consciousness for more than 1 h, (2) central nervous system disease or psychotic disorder, (3) alcohol or other substance abuse, or (4) a diagnosis of any form of dementia.

Neuropsychological tests were administered by trained research staff. Consensus diagnoses were made by an expert team consisting of psychiatrists and neuropsychologists as well as research staff on the basis of all available clinical and neuropsychological data. Finally, 25 individuals with MCI were included in this study.

The present study was approved by the ethics committee of the Institute of Psychology of the Chinese Academy of Sciences. Written informed consent was obtained from each of the participant.

1.2 Assessments

Item memory tests are based on the free recall of pictures and recognition of meaningless figures. For the free recall of pictures task, 15 black and white pictures were shown to participants. These depicted common, easily identified items such as goods for daily use, vehicles, stationery, and natural scenes. Pictures were presented randomly for 4 s each; then, participants were allowed up to 120 s to recall the pictures[17].

In the recognition of meaningless figures task, participants were presented with 20 meaningless figures for 5 s each, and asked to watch carefully and attempt to remember them. In the test phase, participants were presented with 40 figures (20 previously viewed and 20 new) and were asked to judge whether these figures were old or new[17].

The paired-associate learning subtest consisted of 12 word pairs, with 6 easy pairs (semantically related word pairs, *e.g.*, sun-moon) and 6 difficult pairs (in which the words are not related at all, *e.g.*, watermelon-clothes). Each word was composed of 2 Chinese characters. In the study phase, the word pairs were presented auditorily at a rate of 1s per word pair, with intervals of 2 s between two pairs. After the study phase, participants were required to recall the second word of each pair within 5 s after hearing the first word. The study-test procedure repeats twice with different word-pair orders each time. Participants scored 0.5 point for each correct answer for the easy word pairs and 1 point for difficult pairs; total score range was 0 to 27[17].

The associative recall subtest consisted of 6 black and white portraits. In the study phase, each portrait was shown on the computer screen for 9 s. Meanwhile, the surname, job, and hobby of the character in the portrait were presented twice auditorily. Participants were required to remember the associations between the portraits and their characteristics. The inter-stimulus interval was 3 s. In the test phase, the portraits were presented again, and participants were given 30 s to recall the surname, job, and hobby of the character in each portrait. The total score ranged from 0 to 18.

Participants were also administered other neuropsychological tests. Verbal fluency [24], writing fluency, the Trail Making Test (TMT) B [25], and digit span[26] tests were used to assess participants' executive functions and attention. TMT A was used to assess spatial perception and psychomotor speed[25], the Block Design test [26] was used to assess visual-motor integration and constructional abilities, while processing speed was evaluated by the digit symbol subtest from the Chinese version of the Wechsler

Adult Intelligence Scale[26].

1.3 Statistical analysis

Statistical analyses were conducted using Statistical Product and Service Solutions (SPSS) software, version 20.0. *T* tests and Chi-squared distributions were calculated to examine group differences in demographic variables and measures of neurocognitive function. Effect sizes of the group comparisons were calculated in terms of Cohen's *d*[27]. Analyses of variance (ANOVAs) with covariates were conducted to compare group differences in each memory test. A mixed-design ANOVA was conducted to analyze the paired-associate learning subtest, using the Bonferroni correction for multiple comparisons. Degrees of freedom for the within-subjects comparisons were corrected for deviance from sphericity with the Greenhouse-Geisser correction. The receiver operating characteristic (ROC) curve analysis was employed to compare discriminative power for identifying aMCI across each test.

2 Results

2.1 Demographics and neuropsychological tests

As shown in Table 1, no significant group differences were found in gender and ADL. Healthy controls were significantly younger and had significantly higher years of education and MMSE scores than individuals with aMCI. For the other neuropsychological tests, Table 1 shows that individuals with aMCI had significantly lower scores on the verbal fluency, TMT B, digit symbol, Block Design, and similarity tests; they also showed a trend of significantly lower scores on the TMT A and digit backwards tests. The two groups had no significant differences in the writing fluency and digit forward tests.

Table 1 Demographic and descriptive data for the participants groups

	NC	aMCI	F/χ^2	P	Cohen's d
Male：Female	12：16	14：11	0.41	0.25	–
Age (years)	70.79 (6.72)	74.96 (6.54)	6.11	0.03	0.64
Education (years)	14.18 (2.99)	10.12 (4.88)	11.73	0.001	1.04
MMSE	27.96 (1.79)	25.68 (2.36)	16.41	<0.001	1.12
ADL	14.46 (1.04)	14.92 (1.82)	2.66	0.21	0.36
		Neuropsychological tests			
Verbal fluency	23.43 (4.42)	17.90 (3.91)	23.20	<0.001	1.35
Writing fluency	5.24 (1.91)	4.50 (1.90)	1.92	0.17	0.40
TMT A (seconds)	44.00 (14.90)	55.30 (25.44)	3.70	0.06	0.56
TMT B (seconds)	78.11 (39.53)	125.23 (77.79)	7.32	0.01	0.80
Digit symbol	37.18 (7.20)	27.17 (9.43)	18.82	<0.001	1.23
Digit forward	7.86 (1.33)	7.23 (1.74)	2.11	0.15	0.42
Digit backward	4.64 (1.57)	3.91 (1.27)	3.18	0.08	0.52
Block design	30.92 (6.55)	20.63 (6.91)	28.99	<0.001	1.57

Gender ratio between the two groups was tested by Chi Square, while others were analyzed by independent sample *t* test. Mean scores with standard deviation in parentheses; aMCI: Amnestic mild cognitive impairment; MMSE: Mini-mental status exam; NC: Normal controls.

2.2 Comparisons between associative memory and item memory

Due to the significant group differences in age, years of education, and MMSE, these variables were controlled as covariates in the following group comparisons. We first compared group differences in the four episodic memory tests. Table 2 shows that individuals with aMCI performed worse than normal controls in the paired-associate learning, associative recall, and free recall of pictures tests, but not in the recognition of meaningless figures.

Based on the observation of effect size (partial η^2), group differences were larger in the associative memory tests than the item memory tests. In addition, when all the significant group differences of demographics (age, education, and MMSE) and

Table 2 Comparisons between four episodic memory tests in NC and aMCI

	NC			aMCI			F	P	Partial η^2
	N	M	SD	N	M	SD			
Paired-associate learning	28	11.54	2.85	25	4.18	3.00	38.79	<0.001	0.45
Associative recall	28	7.86	3.14	25	2.28	2.44	34.78	<0.001	0.42
Free recall of pictures	28	18.43	2.99	25	13.40	4.05	13.84	0.001	0.22
Recognition of meaningless figures	22	0.48	0.19	23	0.33	0.15	3.27	0.078	0.08

The MMSE, age and education were corrected as covariates; aMCI: Amnestic mild cognitive impairment; NC: Normal controls.

neuropsychological tests (verbal fluency, Trail Making Test B, digital symbol, and Block Design tests) were controlled as covariates, the results showed that individuals with aMCI still demonstrated deficits in the paired-associate learning [$F(1, 35) = 20.95$, $P < 0.001$, $\eta^2_p = 0.37$], and associative recall tests [$F(1, 35) = 27.18$, $P < 0.001$, $\eta^2_p = 0.44$], but not the free recall of pictures [$F(1, 35) = 2.83$, $P = 0.101$, $\eta^2_p = 0.08$] or recognition of meaningless pictures ($F < 1$). Furthermore, when the significant group differences in demographics and cognitive functions and both item memory tests were controlled as covariates, group differences were still significant in the associative memory tests: for the paired-associate learning test, $F(1, 25) = 10.40$, $P = 0.004$, $\eta^2_p = 0.29$, and for the associative recall test, $F(1, 25) = 28.77$, $P < 0.001$, $\eta^2_p = 0.54$. When the same demographic and cognitive functions as well as both the associative memory tests were controlled, however, there was no significant group difference in the item memory tests: for recognition of meaningless figures, $F < 1$, and for free recall of pictures, $F(1, 25) = 1.01$, $P = 0.325$, $\eta^2_p = 0.04$. All of the above results indicate that associative memory was more impaired than item memory in aMCI patients.

2.3 Discriminative power for aMCI

ROC curves for all memory tasks are presented in Figure 1. Discriminative power was calculated separately for each task with the total score. The area under the ROC curve was 0.935($P < 0.001$, confidence interval (CI) [0.866～1.000]) for the paired-associate learning test, 0.902 ($P < 0.001$, CI [0.815～0.989]) for the associative recall test, 0.819 ($P < 0.001$, CI [0.692～0.946]) for the free recall of pictures, and 0.741 ($P < 0.001$, CI [0.593～0.889]) for the recognition of meaningless figures. Both associative memory tests had better discriminative power than the item memory tests, indicating that the associative memory tests would be a more helpful diagnostic tool for aMCI than the item memory tests.

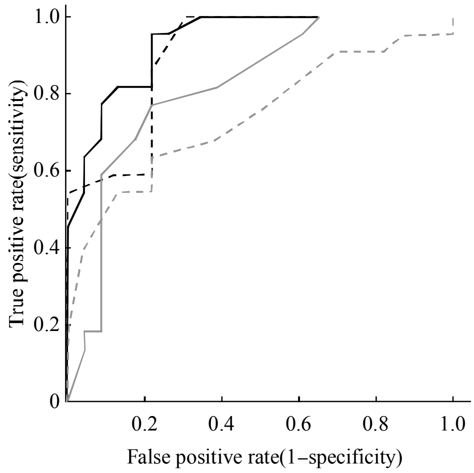

Fig. 1 ROC curve of four episodic tests

—: Paired-association learning; - - : Associative recall; —: Free racall of pictures; - - : Recognition of meaningless figures.

2.4 The decomposed analysis of the paired-associate learning test

We further analyzed the numbers of corrected remembered word pairs in both the easy and difficult levels in the paired-associate learning test. A 2 (NC, aMCI) × 2 (easy and difficult word-pairs) × 3 (first, second, and third trials) mixed analysis of covariance (ANCOVA) with age, education, and MMSE as covariates was conducted to explore whether the two groups performed similarly on the easy and difficult word pairs. The results showed that the main effect of group was significant, $F(1, 48) = 38.71$, $P < 0.001$, $\eta^2_p = 0.45$, indicating that normal controls performed better than aMCI patients across all difficulty levels and trials. Neither the main effect of difficulty level ($F < 1$) nor the main effect of trial were significant, $F(1, 48) = 1.76$, $P = 0.184$, $\eta^2_p = 0.07$. The interactions were not significant in group × trial or in trial × difficulty level (both $F_s < 1$), or in group × difficulty level × trial, $F(2, 47) = 1.24$, $P = 0.300$. However, the interaction between difficulty level and group was significant, $F(1, 48) = 10.20$, $P = 0.002$, $\eta^2_p = 0.18$. Simple effect analysis indicated that the aMCI patients showed lower performance in both easy word-pairs, $F(1, 48) = 32.05$, $P < 0.001$, and difficult word-pairs, $F(1, 48) = 18.57$, $P < 0.001$. As evident in Figure 2 and the examination of the scores and effect sizes, this interaction was due to a larger group difference in the easy word pairs than in the difficult pairs. These results suggest that aMCI participants demonstrated more serious deficits in the semantically related easy pairs.

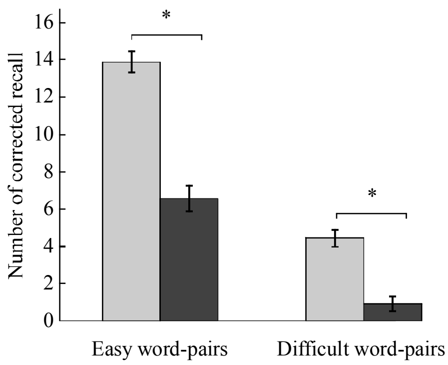

Fig. 2 Number of corrected recall for easy and difficult word-pairs in PALT

Bars depict standard error of the means (SEM). * The group difference was significant ($P < 0.001$). □: HC; ■: aMCI.

3 Discussion

This study presents two main findings. First, we found a serious deficit in associative memory with auditory stimuli in our sample of Chinese aMCI patients, even after controlling for the performance on the item memory tests. Second, contrary to our expectations, aMCI patients showed more impairment in the easy word pairs than that in the difficult word pairs.

Consistent with previous studies [9-10, 12-13], the present study found obvious impairment in associative memory in aMCI patients, even using auditory materials. The differences between aMCI patients and healthy older adults in the associative memory tests were larger than that in the item memory tests. After controlling for the significant group differences in demographic and neuropsychological variables, significant group differences were only found in the associative memory tasks, not the item tasks. More importantly, although it was indicated that failing to remember the items would complicate recall of the associations, we found impairments in associative memory in our aMCI patient group even after controlling for the item memory deficit, in line with previous studies [12-13]. The ROC curve analysis also indicated that associative memory tests have better discriminative power than item memory tests in diagnosing aMCI patients, again in line with a previous study [12]. In combination, these findings suggest that associative memory might be one of the core deficits in aMCI patients, and that associative memory tasks might have better discriminative power in the detection of aMCI[10-11]. These findings have implications for the early screening of aMCI patients.

Previous studies of older adults found that the decline in associative memory might be partly due to difficulties in creating and/or binding cohesive episodes or developing a strategy[28-30]. Naveh-Benjamin and his colleagues proposed that the associative memory decline in older adults might be mediated in part by a difficulty in effectively or spontaneously using relational strategies at encoding and retrieval in comparison with young adults[31-33].

In the present paired-associate learning test, compared to normal older adults, aMCI patients showed deficits in both easy (semantically related) and difficult word pairs (no relationship between the words); in fact, a more serious deficit was found for the easy pairs than the difficult pairs. This indicates that aMCI patients have impairment in using strategies actively to create memory links between the item pairs. In addition, they demonstrated deficits in using the obvious semantic relationship between words that facilitated the creation of memory links in healthy participants. aMCI patients might be impaired to some extent in semantic memory or the quick and efficient processing of semantic knowledge when performing the associative memory tasks.

Abnormal structure and function of some brain areas might be an underlying factor in the associative memory deficits in individuals with aMCI. The hippocampus and entorhinal cortex are especially important for associative memory[12], however, variety of studies have found atrophy of the hippocampus and entorhinal cortex in aMCI patients [34-36]; these neuroanatomical changes might result in associative memory deficits. Moreover, several studies have reported that during encoding novel associations, patients with MCI and AD began to show abnormal patterns of activation in associative memory-related brain areas. Dickerson *et al.*[37] (2005) reported that the AD group showed less activation in the hippocampus and entorhinal cortex than controls, while the MCI group showed more activation in the hippocampus than controls during a face-surname associative encoding task. The researchers explained that patients showed increased activation in the medial temporal lobe during the early stages of AD, but activation decreased as the disease progressed. A recent study investigated the associative encoding in aMCI and older controls while controlling for item encoding. They found that associative memory impairment in aMCI might be related to decreased activation in the left anterior hippocampus[13].

Another previous study found that cognitive support (subject-performed tasks) could facilitate the formation of episodic associations in individuals with aMCI, even without the support of pre-existing semantic knowledge[38]. Our recent meta-analysis found that individuals with MCI could obtain benefits in episodic memory during cognitive intervention, and that those benefits could be maintained over time [39]. Naveh-Benjamin *et al.*[32](2007) suggested that adopting verbal relational strategies during the study and test phases would facilitate older adults' memory of new knowledge. By consciously learning and spontaneously using strategies at encoding or retrieval, individuals with aMCI could reduce their difficulty in creating or binding cohesive episodes; their associative memory performance may also improve.

4 Limitations

This study presents some limitations. First, as with most other studies in this area, the present study involved a relatively small number of participants, and those participants might have included both single and multiple domain aMCI individuals. Future studies conducted in multiple centers with larger samples may reduce this selection bias and provide stronger evidence for their conclusions. Second, the performance of aMCI patients is very low in the difficult word pairs of the paired-associate learning test. We cannot rule out the possibility that the smaller group difference in difficult word pairs relative to easy word pairs is due to a scale effect [40]. Third, the associative and item memory tests compared in the current study were not matched in some aspects, such as the number of the items or associations, recall, or recognition.

5 Conclusion

The present study investigated associative memory deficits with auditory materials in a sample of Chinese aMCI patients using native tools. This impairment was found to be more serious than item memory in aMCI patients. The impairment of associative memory in aMCI patients might not only be the result of a dysfunction in the use of strategies to create memory links between item pairs, but also a deficit in semantic memory, or the quick and efficient processing of semantic knowledge when performing the associative memory tasks. In the present study, the associative memory tests had better discriminative power than item memory tests in the identification of aMCI patients. Therefore, including associative memory tasks in future neurocognitive assessment protocols could help to improve the diagnostic "hit rate" for aMCI, especially in a region like China with a large population of potential aMCI patients.

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轻度认知损伤患者的联系记忆损伤特征 *

王鹏云 [1, 2] 李 娟 [1)**] 李会杰 [1] 李 冰 [1, 2] 李 欣 [1, 2] 周 婷 [1, 2]

([1] 中国科学院心理研究所心理健康重点实验室，老年心理研究中心，北京 100101；[2] 中国科学院大学，北京 100049)

摘要 遗忘型轻度认知损伤患者(aMCI)在项目记忆和联系记忆上都有损伤．本文通过临床记忆量表中的项目记忆和联系记忆测验，研究 aMCI 的联系记忆是否比项目记忆有更显著的损伤．另外，通过分析配对联想学习测验，进一步研究 aMCI 联系记忆损伤的特点．25 名 aMCI 和 28 名健康老人参与了两个联系记忆测验(配对联想学习测验和联想回忆测验)和两个项目记忆测验(图像自由回忆和无意义图形再认)，aMCI 患者在联系记忆测验上表现出了更显著的损伤，即使控制了项目记忆的损伤，aMCI 的联系记忆仍然比健康老人显著降低．另外，ROC 分析表明联系记忆测验比项目记忆测验对 aMCI 病人有更高的区分度．对配对联想学习测验的分析表明，相对于健康老人，aMCI 患者在记忆有语言联系的词对要比记忆无语义联系的词对更为困难．本研究进一步表明 aMCI 患者的联系记忆比项目记忆有更大的损伤．相对于健康老人，aMCI 患者不仅难以在两个无关项目间创建记忆连接，而且在有效利用项目间本身的语义联系方面存在更大的损伤．联系记忆测验比项目记忆测验对 aMCI 患者有更高的区分度．在神经心理评估中增加联系记忆测验，能更加有效地识别 aMCI 患者．

关键词 轻度认知损伤，联系记忆，项目记忆

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** 通讯联系人．

Tel: 010-64861622, E-mail: lijuan@psych.ac.cn

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