Learning and Error Patterns in the Chinese Verbal Learning Test in Subjects with Mild Cognitive Impairment and Normal Elderly

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Abstract-

Purpose: The discrimination between normal elderly (NC) and those with mild cognitive impairment (MCI) is of clinical relevance since the conversion from MCI to Alzheimer dementia (AD) is high.

Methods: This study enrolled 216 amnestic MCI patients and 103 NC from our memory clinics and assessed whether the learning curve, recall and cued scores, as well as error patterns from the Chinese Version Verbal Learning Test (CVVLT) helped to distinguish between these two groups.

Results: Our results revealed that subjects with MCI had a lower rate of acquisition and deceleration of learning in the learning curve. The MCI group also showed a lower retention rate and recall scores as compared with the NC group. Further, the error patterns offered discrimination values between the two groups in total number of perseverations, intrusion in the cued recall, as well as prototypic and unrelated errors in recognition. An inverse correlation was seen between memory scores and error patterns.

Conclusion: This study suggests that by combining the learning and error patterns from the verbal memory test, patients with MCI can be better differentiated from normal elderly.

Key Words: verbal learning test, education, memory, mild cognitive impairment

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INTRODUCTION

Mild cognitive impairment (MCI) represents a wide spectrum and the clinical differentiation can be difficult. The discrimination between normal elderly and those with MCI is of clinical relevance since many elderly individuals frequently have memory complaints, and correct identification of MCI with memory complaints helps to set up clinical monitoring and treatment plans. Understanding the memory processes disturbed in MCI

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can also help to separate early dementia from normal aging processes, since an average annual conversion rate to Alzheimer dementia (AD) has been found to be around 12% [1] in amnestic MCI.

Many verbal learning tasks have been developed and widely used as instruments for evaluating episodic memory such as the Hopkins Verbal Learning Test [2], the Word List Recall Test from the Consortium to Establish a Registry for Alzheimer's Disease [3], the Neuropsychological Assessment Battery List Learning Test [4] and the California Verbal Learning Test (CVLT-II)[5]. Recent studies have shown that the risk of progressing from normal to MCI is considerably greater among those with lower scores on CVLT-II tests [6] (hazard ratio for a 1-SD decrease in the CVLT-II, 0.55; $p<0.001$) and that the total learning score from the CVLT-II ranked highest in terms of distinguishing MCI from normal aging among several batteries [7].

In addition to the 16-item version of the CVLT-II, there is a nine-item version that is less sophisticated and time consuming [8]. This short version (CVLT-SF) consists of three words from three different semantic categories. It has good sensitivity and specificity in detecting memory deficits in AD patients [8] and the delayed recall score has been found to correlate well with changes in the hippocampus [9]. A Chinese Version Verbal Learning Test (CVVLT) has been developed by our group. The CVVLT was not directly translated from the CVLT-SF considering the differences in word familiarity, frequency, phoneme and cultural driven factors. It is pertinent for memory measurement in this study since it does not require a long testing time, making it suitable for older subjects with memory complaints. It has been validated in discriminating AD from controls [10].

Previous studies have shown that normal aging is accompanied with gray matter and white matter loss, specifically in the prefrontal regions followed by temporal areas [11], which usually causes specific error patterns in performing verbal memory tests [12]. Patients with AD often demonstrate a severe impairment in learning curve and recognition with prominent perseveration and intrusion [13]. A recent study showed that free and cued recall tests were able to distinguish patients at an early stage of AD from MCI non-converters [14].

The present study aimed to detect the differences in error patterns, in addition to correct recall, between patients with MCI and normal elderly using the CVVLT. Since the MCI group might reflect a continuum between AD and NC, we hypothesized that error patterns, in addition to the recall scores, may differentiate the MCI group from the NC group if detailed neuropsychological testing was applied.

METHODS

Instrument

The Chinese Version Verbal Learning Test (CVVLT) consists of nine two- character nouns presented over four learning trials, with recall assessed after 30-second and 10-minute delays, and a delayed word recognition test[10]. Each of the items fall within one of the following three categories: fruit, clothes, and transportation. The recognition test is composed of 27 word-lists, with nine target words, nine distracter prototypes, and nine words unrelated to the learning list.

Subjects

Three hundred and nineteen (319) subjects were recruited from the memory clinics of the Department of Neurology of Taipei Veterans General Hospital and Kaohsiung Chang Gung Memorial Hospital. These included 216 patients with a clinical diagnosis of MCI and 103 NC elderly. The human ethics committee of both hospitals approved the study protocol.

Neurologists first interviewed all of the subjects. The diagnosis of MCI was based on the results of clinical interviews, neurologic examinations, neuro-psychological tests, laboratory findings, and neuro-imaging evaluation. MCI patients met the criteria based on Petersen et al.'s study [15] and revised criteria by the Stockholm consensus group [16] including: (1) presence of memory complaints (preferably corroborated by an informant); (2) objective measure of impaired memory function was determined by CVVLT 10-minute recall scores below 6 based on our previously published cutoff value for AD[10]; (3) maintained activities of daily living - the patient should be able to maintain professional, social and familial activities according to clinical judgment. We also used the Clinical Dementia Rating (CDR) scale. The CDR rates the subject's impairments in six categories - memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care - on a 5-point scale (0, 0.5, 1, 2, and 3). Only patients with CDR 0 and 0.5 were included in the analysis; and (4) preserved general cognitive function, according to both the clinician's impression and a Mini-Mental State Examination (MMSE)[17] score above a cut-off value (MMSE ≥ 24) within the reference limit in Taiwan[18].

The NC controls were volunteers or the spouses of the patients. All of them received the same standard clinical evaluation used for MCI subjects. None had a history of neurologic or psychiatric disorders, or showed any evidence of impairment in the neurologic examination. All of the NC controls had a CDR score of 0.

Procedures and scoring

The examiner read the nine-word list aloud at one-second intervals in a fixed order over four learning trials (CVVLT 1 to 4). After each trial, the subject was asked to recall as many words as he/she could in any order. After 30 seconds (CVVLT-30s) and 10 minutes (CVVLT-10m), the subject was again asked to recall the list. The number of correct items, intrusions, and perseveration errors were recorded in each trial. Intrusion was defined as the subject giving an incorrect item not present in the list, while perseveration errors meant that a subject gave a correct item more than once. On the cued recall trials, subjects were asked to recall the nine-word lists as the examiner specified each category (i.e., fruit, clothes, and transportation).

The CVVLT ended with a recognition task. As each word on a 27-word list was read aloud, the subject indicated whether it was a target word or a distracter. Some distracters shared semantic categories with the target words (prototypic) while others sounded alike (unrelated categories). Intrusions were scored separately on free and cued recall trials whereas perseverations were tallied over all trials. The total correct recall scores from the first 4 trials were also calculated (CVVLT-total) for further analysis.

Statistical analysis was done using the Statistical Package for Social Sciences (SPSS) software package (version 13 for Windows®, SPSS Inc, Chicago, IL). Comparisons between the MCI and NC group were analyzed using the chi-square test for categorical data, analysis of variance (ANOVA) followed by the Tukey post hoc test for numerical data with normal distribution or Kruskal-Wallis followed by the Dunn post hoc test for numerical data when normal distribution could not be assumed. Comparisons of neuropsychological data involving the two groups were done using the Student's *t* test for parametric analysis and Mann-Whitney test for nonparametric analysis. Pearson correlation analysis was used to check the correlations between the scores of the CVVLT and other demographic data studies. A value of p less than 0.05 was considered statistically significance in this study.

RESULTS

Of the 319 subjects included, there were 184 males and 135 females. Their mean age was 74.4 ± 9.2 years (range: 50-97 years) and their mean education level was 11.4 ± 4.4 years of schooling (range: 0-18 years). There were 103 NC and 216 with MCI. Among the MCI patients, 16 had CDR 0 and 200 had CDR 0.5. Table 1 shows the detailed demographics and performances on the CVVLT of the subjects. In demographic comparison with the NC group, the MCI group was older and had lower educational levels ($p<0.01$). Sex distribution showed that the MCI group contained more men than women (chi-square value 7.648).

CVVLT in the NC elderly

Effects of age on correct patterns

Age had a significant effect in the performance on the CVVLT in the 103 NC (Table 2). Age was inversely correlated with all learning and delayed recall scores in NC subjects (CVVLT-1, r = -0.320, $p<0.001$; CVVLT-2, r = -0.320, $p<0.001$; CVVLT-3, r = -0.474, $p<0.001$; CVVLT-4, r = -0.361, $p<0.001$; CVVLT-30s, r = -0.310,

Table 1. Demographic data and scores on the Chinese Version Verbal Learning Test

	Normal Controls (n=103)	Mild Cognitive Impairment (n=216)
Age range	51-91 (69.4±10.2)	55-97 (76.7±7.7)**
Sex (M/F)	48/55	136/80**
Education	3-18 (13.16±3.6)	0-18 (10.7±4.5)**
Mini-Mental State Examination	22-30 (28.6±1.4)	24-30 (27.0±1.5)**
Clinical dementia rating	0	0.46±0.1**
Chinese Version Verbal Learning Test		
Trial 1	5.0±1.5	3.5±1.3**
Trial 2	6.9 ±1.3	4.9±1.3**
Trial 3	7.7±1.3	5.5±1.4**
Trial 4	8.0±0.9	5.9±1.5**
Total recall	27.5±4.1	19.9±4.5**
30-second recall	8.0±1.1	5.1±1.7**
10-minute recall	8.0±1.2	4.0±2.0**

Data are presented as mean±SD (standard deviation); ** $p<0.01$ compared to controls

$p<0.05$; CVVLT-10m, $r=-0.265$, $p<0.05$). All NC subjects were first categorized into three age groups: ≤65, 65-69, and ≥70 years. ANOVA revealed a significant difference among these groups in the MMSE and CVVLT learning trials (MMSE, F=4.87, $p=0.009$ CVVLT-1, F=4.71, $p=0.011$; CVVLT-2, F=4.53, $p=0.013$; CVVLT-3, F=10.88, $p=0.000$; and CVVLT-4, F=4.92, $p=0.009$) and recall scores (CVVLT-30s, F=4.43, $p=0.014$; CVVLT-10m, F=2.63, $p=0.046$).

Post-hoc analysis of the CVVLT scores showed that subjects in the ≤65 and 65-70 age groups did not have significant differences in learning (CVVLT 1 to 4) or recall scores. Thus, only two age groups, <70 and ≥70 years, were used in subsequent analyses to examine the effect of age.

Effects of age on error patterns

Age showed non-significant correlations with recall scores by cueing ($r=-0.181$, $p=0.051$) and recognition ($r=-0.136$, $p=0.14$). T-tests showed that the recall scores by cueing or recognition were not significantly different between the <70 and ≥70 year-old age groups.

Error analysis in the two age groups showed no significant differences in the intrusion and perseveration errors from CVVLT 1 to 4, CVVLT-total, CVVLT-30s, CCVLT-10m and recall from cueing. In the recognition test, only prototypic but not unrelated errors were significantly higher in the ≥70 age group ($p<0.05$).

Effects of education on learning and error patterns

Educational levels had a mild but significant correlation with CVVLT learning scores (CVVLT-2, $r=0.210$, $p<0.05$; CVVLT-4, $r=0.187$ $p<0.05$). The educational level was not correlated with errors in learning trials 1 to 4, CVVLT-total, CCVLT-10m and recognition. However, it was inversely correlated with perseveration errors in CVVLT-30s ($r=-0.191$, $p=0.04$) and perseveration errors ($r=-0.21$, $p=0.02$) in cued recall. We further divided the educational levels into three groups (Group 1: 0-6 years; Group 2: 7-11 years; and Group 3: ≥12 years) for analysis. In learning trials 1 to 4, CVVLT-total, CVVLT-30s, CCVLT-10m, cued and recognition recall, only the highest education group (Group 3) had significantly higher scores in CVLLT-2 than the other two groups ($p=0.03$). The three educational groups showed no differences in the error pattern analysis.

Interaction of age and education

According to previous findings by ANOVA for age groups, 70 years old was chosen as the boundary to compare the scores of CVVLT-total in the three educational levels. Two-way between groups ANOVA showed that only age (p<0.001) but not education (p=0.074) showed a significant effect on the CVVLT-total scores.

Comparing the learning CVVLT in the curves of MCI and NC control groups

Multivariate ANOVA was performed to test the effects of age and education in the comparison of the performance of CVVLT in the MCI and NC groups. Because both age and education had significant influences on the performance of CCVLT scores, comparisons between the two groups was done by dividing them into two age groups and three educational groups (Table 2).

In the 4 learning trials, the MCI group had lower scores than the controls across all scores (p<0.001). The retention rate was calculated by dividing scores of CVVLT-30s or CVLLT-10m by those in CVVLT-4. The results showed that the MCI group had a retention rate of 0.9 at 30 seconds (NC=1) which dropped to 0.7 after 10 minutes (NC=1). MCI patients also had lower scores in cued recall (p<0.001). In the recognition test, the MCI group had lower scores as compared with the NC group

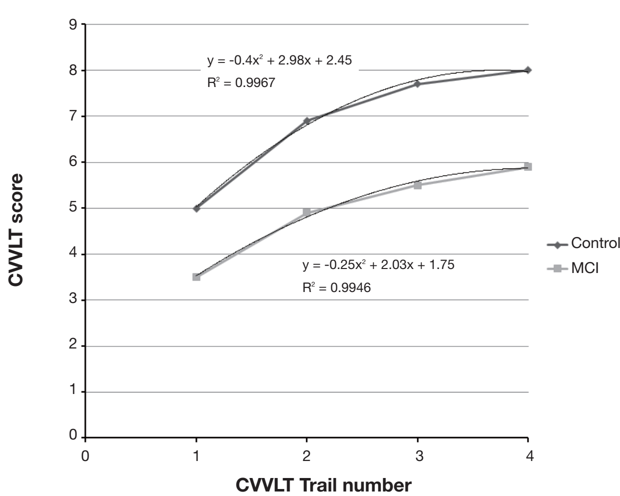

Figure 1. Learning curves in the controls and the subjects with mild cognitive impairment in four trials. The equation of each group is labeled as Y = Cx^2+ Bx+ A

X= Chinese Version Verbal Learning Test (CVVLT) Trail number; Y= CVVLT score

only in education Group 3.

To detail the learning difficulties, we drew learning curves for patients with MCI and NC controls (Figure 1). In the CVLT manual, the rate of learning across the four trials is calculated as the slope of a simple linear function. However, and in accordance with previous studies [19], we found that our data were best fit by a quadratic model $Y = A + Bx + Cx^2$ (r^2 >0.99 for the learning curves of controls and MCI subjects, Figure 1). The equations are listed in the figure.

Error patterns in MCI and compared with NC group (Table 3)

Table 3 lists the error patterns in the MCI and NC groups divided into two age and three educational groups. The control group had significantly higher perseveration errors in CVVLT-total in education Group 2 (p<0.05) than the MCI group, but not in intrusion errors. In CVVLT-30s and CVVLT-10m, perseveration errors were not found in the NC group. In the MCI group, those aged less than 70 years and with more than 12 years of education showed higher perseveration errors in CVVLT-30s. For subjects younger than 70, the MCI group showed significantly higher intrusion errors in the education level >12 years.

In the recognition errors, the MCI group showed more prototypic and unrelated types of error as compared with the NC group. In cued recall, the MCI group had higher intrusion errors compared with the NC group, but the perseveration errors were only higher in the education group >12 years. In subjects with MCI, the scores in error patterns (i.e. intrusions and perseverations in recognition and cued recall) were inversely correlated with scores in the recall trials (i.e. CVVLT-total, CVVLT-30s, CVVLT-10m). The results are shown in Table 4.

DISCUSSION

The main goal of this study was to understand the learning curve, recall and error patterns using a verbal memory test in normal elderly subjects and subjects with MCI. Our study revealed that in the NC group, age but

Table 2. Comparison between patients with mild cognitive impairment and controls by education and age groups

		All ages		*Age <70*		*Age ≥70*	
	Education	Control N=103	MCI N=216	Control N=49	MCI N=37	Control N=54	MCI N=179
CVVLT-1	0-6	4.5 (1.6)	3.5 (1.2)*	5.0(1.8)	3.7 (1.5)	4.0 (1.3)	3.4 (1.1)
	7-11	5.1 (1.4)	3.4 (1.3)**	5.8 (2.2)	4.1 (1.3)*	4.8 (0.7)	3.3 (1.3)*
	≥12	5.0 (1.5)	3.6 (1.4)**	5.4 (1.4)	4.4 (1.3)*	4.6 (1.4)	3.4 (1.4)**
CVVLT-2	0-6	6.1 (1.5)	4.9 (1.2)*	7.0 (0.9)	5.5 (1.0)*	5.1 (1.5)	4.8 (1.3)
	7-11	7.4 (1.0)	4.9 (1.2)**	8.0 (1.2)	5.3 (2.0)*	7.1 (0.8)	4.8 (1.1)**
	≥12	7.0 (1.3)	4.8 (1.4)**	7.2 (1.2)	5.7 (1.6)**	6.5 (1.3)	4.6 (1.4)**
CVVLT-3	0-6	7.2 (1.3)	5.7 (1.2)**	7.8 (1.0)	6.1 (1.0)*	6.5 (1.2)	5.6 (1.2)
	7-11	7.6 (1.2)	5.4 (1.4)**	8.0 (0.8)	6.0 (2.4)*	7.4 (1.4)	5.2 (1.2)**
	≥12	7.7 (1.3)	5.6 (1.5)**	8.2 (0.9)	6.1 (1.6)**	7.1 (1.4)	5.5 (1.5)**
CVVLT-4	0-6	7.5 (1.2)	6.2 (1.3)*	7.8(1.2)	5.8 (1.3)*	7.2 (1.2)	6.3 (1.3)
	7-11	8.0 (1.0)	5.5 (1.4)**	8.5 (0.6)	6.0 (1.7)*	7.8 (1.0)	5.5 (1.4)**
	≥12	8.1 (0.9)	6.0 (1.6)**	8.4 (0.7)	6.6 (1.6)**	7.7 (0.9)	5.8 (1.5)**
CVVLT-total	0-6	25.3 (4.3)	21.3 (3.7)**	25.7 (3.0)	21.1 (3.7)*	22.8 (4.2)	20.1 (3.7)
	7-11	28.1 (3.7)	19.2 (4.4)**	30.3 (3.4)	21.4 (6.9)*	27.0 (3.5)	18.8 (3.9)**
	≥12	27.7 (4.1)	20.0 (4.9)**	29.2 (3.3)	22.8 (4.3)**	25.8 (4.2)	19.4 (4.8)**
CVVLT_30_second	0-6	7.4 (1.5)	5.3 (2.0)**	7.8 (1.6)	5.3 (1.4)*	7.0 (1.4)	5.2 (2.1)
	7-11	8.0 (1.3)	4.9 (1.4)**	8.6 (0.5)	5.6 (2.2)*	7.6 (1.5)	4.8 (1.2)**
	≥12	8.1 (1.0)	5.1 (1.8)**	8.5 (0.7)	5.6 (1.4)**	7.7 (1.2)	5.1 (1.8)**
CVVLT_10 minute	0-6	7.6 (1.1)	4.3 (2.2)**	8.0 (0.9)	4.1 (1.9)*	7.2 (1.2)	4.3 (2.2)*
	7-11	7.9 (1.0)	3.7 (1.9)**	8.3 (1.0)	4.9 (1.2)**	7.8 (1.0)	3.5 (2.0)**
	≥12	8.1 (1.2)	4.0 (2.0)**	8.4 (0.7)	4.4 (1.9)**	7.7 (1.6)	3.9 (2.1)**
30sec_ Retention	0-6	1.0 (0.1)	0.9 (0.3)*	1.0 (0.1)	0.9 (0.3)	1.0 (0.2)	0.8 (0.3)
	7-11	1.0 (0.1)	0.9 (0.2) **	1.0 (0.1)	0.9 (0.2)	1.0 (0.1)	0.9 (0.2)
	≥12	1.0 (0.1)	0.9 (0.3)**	1.0 (0.7)	0.9 (0.2)**	1.0 (0.1)	0.9 (0.3)**
10min_ Retention	0-6	1.0 (0.1)	0.7 (0.3)**	1.0 (0.1)	0.7 (0.3)**	1.0 (0.2)	0.7 (0.3)*
	7-11	1.0 (0.1)	0.7 (0.4)**	1.0 (0.1)	0.8 (0.1)	1.0 (0.1)	0.6 (0.4)**
	≥12	1.0 (0.1)	0.7 (0.3)**	1.0 (0.1)	0.7 (0.3)**	1.0 (0.2)	0.7 (0.3)**
Cued_recall	0-6	7.8 (1.3)	5.2 (1.9)**	8.0 (1.3)	5.0 (2.1)*	7.5 (1.4)	5.3 (1.8)*
	7-11	7.9 (1.2)	4.9 (1.9)**	9.0 (0.0)	5.0 (1.9)*	8.1 (0.8)	4.8 (1.9)**
	≥12	8.4 (0.8)	5.0 (2.1)**	8.5 (0.7)	5.3 (2.0)**	8.2 (0.9)	4.9 (2.1)**
Recognition	0-6	8.5 (0.7)	8.3 (0.8)	8.8 (0.4)	8.2 (0.7)	8.2 (0.8)	8.3 (0.8)
	7-11	8.7 (0.9)	8.1 (1.2)	7.5 (1.7)	8.3 (1.0)	8.5 (1.1)	8.1 (1.3)*
	≥12	8.8 (0.4)	7.8 (1.5)*	8.8 (0.4)	8.1 (1.4)*	8.9 (0.4)	7.7 (1.5)**

**$p<0.01$; *$p<0.05$ when comparing MCI with age and education matched controls

Abbreviations: CVVLT= Chinese Version Verbal Learning Test; MCI= mild cognitive impairment;

For the three education groups: n=66 for the 0-6 years group, n=60 for the 7-11 years group, and n=193 for the ≥12 years group.

Table 3. Error pattern analysis between patients with mild cognitive impairment and controls by education and age groups

		All ages		*Age <70*		*Age ≥70*	
	Education	Control N=117	MCI N=219	Control N=63	MCI N=40	Control N=54	MCI N=179
CVVLT-total_p	0-6	4.08(4.72)	3.44(3.21)	4.33(3.67)	4.17(3.56)	3.83(5.95)	3.24(3.12)
	7-11	6.41(7.11)	2.63(3.49)*	5.50(5.26)	2.86(4.67)*	6.88(8.18)*	2.60(3.32)
	≥12	4.30(4.93)	2.80(3.28)*	4.70(4.76)	4.52(4.00)	3.78(5.16)	2.42(2.99)
CVVLT-total_i	0-6	2.00(2.17)	2.04(2.88)	1.50(2.51)	2.33(1.83)	2.50(1.87)	1.95(3.13)
	7-11	0.83(0.94)	1.37(1.38)	0.25(0.50)	1.14(0.90)	1.13(0.99)	1.40(1.45)
	≥12	1.14(1.65)	1.68(2.35)	1.06(1.60)	3.19(3.43)**	1.25(1.72)	1.34(1.90)
CVVLT_30s_p	0-6	2.33(2.61)	0.85(1.42)	2.33(2.94)	1.17(1.53)	2.33(2.50)	0.76(1.39)*
	7-11	0.75(1.49)	0.57(1.23)	0.50(1.00)	1.00(1.53)	0.88(1.73)	0.50(1.17)
	≥12	0.30(0.57)	0.94(1.74)	0.77(1.57)	2.14(2.63)*	0.73(1.62)	0.67(1.36)
CVVLT_30s_i	0-6	0.33(0.49)	0.72(1.05)	0.17(0.41)	0.83(0.72)	0.50(0.55)	0.69(1.14)
	7-11	0.17(0.39)	0.39(0.67)	0.00(0.00)	0.57(0.79)	0.25(0.46)	0.36(0.66)
	≥12	0.30(0.57)	0.65(0.96)*	0.30(0.58)	0.95(1.40)*	0.30(0.56)	0.58(0.83)
CVVLT_10m_p	0-6	1.33(2.10)	0.80(1.25)	0.83(0.98)	0.92(1.51)	1.83(2.86)	0.76(1.19)
	7-11	0.67(1.07)	0.67(1.41)	0.50(1.00)	0.57(1.13)	0.75(1.17)	0.69(1.46)
	≥12	1.09(2.01)	0.67(1.41)	1.28(2.25)	0.95(1.88)	0.83(1.65)	0.61(1.30)
CVVLT_10 m_i	0-6	0.75(0.97)	1.09(1.17)	0.50(1.22)	1.42(1.44)	1.00(0.63)	1.00(1.08)
	7-11	0.25(0.45)	0.55(0.87)	0.25(0.50)	1.00(1.00)	0.25(0.46)	0.48(0.83)
	≥12	0.40(0.59)	0.87(1.09)**	0.34(0.55)	0.95(1.12)*	0.48(0.64)	0.85(1.09)
Recognition_ proto	0-6	0.08(0.29)	1.54(1.93)*	0.17(0.41)	1.75(1.96)*	0.00(0.00)	1.48(1.94)**
	7-11	0.58(0.90)	0.51(2.82)**	0.50(1.00)	2.57(2.70)	0.63(0.92)	2.14(2.24)*
	≥12	0.28(0.76)	1.91(2.11)**	0.11(0.32)	2.10(2.39)**	0.50(1.06)	1.86(2.06)**
Recognition_ unrelat	0-6	0.00(0.00)	0.46(1.46)*	0.00(0.00)	0.25(0.45)	0.00(0.00)	0.52(1.64)
	7-11	0.00(0.00)	0.51(1.02)**	0.00(0.00)	0.29(0.76)	0.00(0.00)	0.55(1.06)*
	≥12	0.02(0.15)	0.38(1.02)**	0.00(0.00)	0.62(1.43)	0.05(0.22)	0.33(0.90)**
Cue recall_p	0-6	0.58(1.73)	0.13(0.39)	1.00(2.45)	0.00(0.00)	0.17(0.41)	0.17(0.44)
	7-11	0.08(0.29)	0.29(0.89)	0.00(0.00)	0.00(0.00)	0.13(0.35)	0.33(0.95)
	≥12	0.01(0.10)	0.31(1.04)*	0.00(0.00)	0.19(0.40)*	0.03(0.16)	0.34(1.13)*
Cue recall_i	0-6	0.67(1.37)	2.02(2.11)*	0.67(1.63)	2.67(2.10)*	0.67(1.21)	1.83(2.09)
	7-11	0.33(0.65)	1.78(2.94)*	0.50(1.00)	1.71(1.80)	0.25(0.46)	1.79(2.61)*
	≥12	0.46(0.80)	1.93(2.25)**	0.43(0.84)	2.33(3.12)*	0.50(0.75)	1.84(2.01)**

**p<0.01; *p<0.05 when comparing MCI with age and education matched controls

Abbreviations: CVVLT= Chinese Version Verbal Learning Test; MCI= mild cognitive impairment; i= intrusion; p= perseveration; Recog_proto= prototypic error in recognition; Recog_unrelat= unrelated error in recognition; CVVLT_30s= 30-second recall; CVVLT_10m= 10-minute recall.

For the three education groups: n=66 for the 0-6 years group, n=60 for the 7-11 years group, and n=193 for the ?12 years group.ns: CVVLT= Chinese Version Verbal Learning Test; MCI= mild cognitive impairment;

For the three education groups: n=66 for the 0-6 years group, n=60 for the 7-11 years group, and n=193 for the ≥12 years group.

Table 4. Correlation between scores in recall and error patterns in the mild cognitive impairment group

	CVVLT-total	CVVLT-30s	CVVLT-10m
Prototypic error in recognition	r=-0.246 **	r= -0.349 **	r= -0.442 **
Unrelated error in recognition	r=-0.139 *	r= -0.261 **	r= -0.282 **
Perseveration error in cued recall	r= 0.324 **	r= 0.159 *	r= 0.138 *
Intrusion error in cued recall	r= -0.101	r= -0.102	r= -0.140 *

r= Pearson correlation coefficient; CVVLT= Chinese Version Verbal Learning Test; CVVLT-total= total scores from trial 1 to 4; CVVLT_30s= 30-second recall; CVVLT_10m= 10-minute recall.

**p<0.01; *p<0.05

not educational level had a great influence on the learning curve and recall scores. Subjects with MCI presented consolidation deficits reflected in the low retention rate after 30-second and 10-minute recall, which suggests the pathophysiology is the same in MCI as in AD [20]. More importantly, the different error patterns in the two groups also offered discrimination values, in that the NC group had higher perseverations in the learning trials but not intrusion in the educational group ≥7 years. The MCI group, in contrast, showed more intrusion error in recognition and cue recall.

As expected, the MCI group had lower scores in the learning trials, short and delayed recall across all ages and educational sub-groups as compared with NC subjects. Furthermore, this study demonstrated the low retention rate of both CVVLT-30s and CVVLT-10m in MCI subjects. Since delayed recall precedes the recognition test, the low retention rate is related to higher forgetting rates rather than the influence of the distracter list. We also observed that MCI patients benefited little from external organization cues and recognition tests. The combination of poor performance in delayed recall, cued recall, and recognition tests suggests that the memory deficits in MCI are related to both encoding and self-retrieval deficits [21]. The NC group showed a much higher retention rate in delayed recall than the MCI group and significantly benefited from cues and recognitions. These findings support the position that MCI represents an early point of decline on the continuum of AD that is different from normal aging.

The NC group appeared to have more perseveration errors as compared with the MCI group. Given our age related findings on the list learning task and the older age of the MCI group, we already controlled the effect of aging during the analysis. Whether the higher number of perseveration errors in the NC group reflects a state of impaired registration of the word list in the MCI group, and therefore lower perseveration errors, remains to be established. However, the effects could be the interference of prefrontal lobe function related to aging. Huh and colleagues [22] suggested that degeneration of the frontal lobes may contribute to response errors in older adults, while degeneration and atrophy of the prefrontal lobe has been recognized in neuroimaging studies for the aging process [23,24]. A link between prefrontal lobe dysfunction and perseveration errors has also been established in other disease models such as schizophrenia[25], methamphetamine encephalopathy[26] and epilepsy [27]. Therefore, perseveration errors related to aging must also be considered during data interpretation and the adjustment for age effects on neuropsychological tests are particularly important.

From our learning curve equation ($Y = A + Bx + Cx^2$), the coefficient B represents the rate of acquisition and the coefficient C the rate of deceleration of learning [19]. The intercept component was not considered in the analysis as it represents the number of words recalled in a nonexistent trial zero. Curve estimated parameters showed differences for the B coefficient, meaning the control subjects learned faster than the MCI patients. The C coefficient was also significantly different between controls and the MCI group. The earlier deceleration of learning seen in the controls suggests that this group reaches a maximum list learning capacity faster than the patient group. The data again revealed the impairment of learning efficiency in the MCI group.

Intrusions are generally useful in diagnosing AD[28,29]. From our study results, significant differences between the NC and MCI groups in intrusion errors were reflected more robustly in the cued recall test as compared to short or long recall. In addition, error patterns in the recognition test including the prototypic and unrelated errors also discriminated the two groups better. The inverse correlation between memory scores and errors also showed that impairment in the memory domain does indeed interfere with the performance in recall and cues. Patients with MCI can be better differentiated from NC by a combination of recognition and cue recall error analysis rather than errors in short or long delays.

The first limitation of our study is the objective criteria for MCI using the CVVLT-10m score. Since we already validated CVVLT using CVVLT-10m cutoff value of 6 to discriminate AD with NC, the similar criteria might have chosen patients with early AD. The MCI subgroup in this study might perform toward the floor effect. Second, this was a cross-sectional study, thus we could not provide any predictive value in terms of the conversion rate from amnestic MCI to AD. A longitudinal data on these MCI patients might be necessary. According to the International Working Group on MCI [30], the diagnosis of MCI requires evidence of cognitive deterioration shown by either objectively measured decline over time and/or a subjective report of decline by self and/or informant in conjunction with objective cognitive deficits over time on objective cognitive tasks. To demonstrate a decline over time requires repeated administration of cognitive tests. Repeated administration of a neuropsychological test is associated with confounding factors that must also be taken into consideration.

In conclusion, the MCI subjects presented inefficient learning, low retention rates and more intrusion errors in recall trials as compared with the NC group. Aging was only associated with perseveration but not other error patterns. A detailed objective verbal memory test is mandatory to identify MCI from normal aging.

Conflict of interest declaration: none.

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REFERENCES

1. Mitchell AJ, Shiri-Feshki M. Temporal trends in the long term risk of progression of mild cognitive impairment: a pooled analysis. J Neurol Neurosurg Psychiatry 2008;79: 1386-1391.
2. Brandt J, Benedict RHB. Hopkins Verbal Learning Test-Revised Professional manual. 2001, FL: Psychological Assessment Resources.
3. Morris JC, Heyman A, Mohs RC, Hughes JP, van Belle G, Fillenbaum G, Mellits ED, Clark C. The Consortium to Establish a Registry for Alzheimer’s Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer’s disease. Neurology 1989;39:1159-1165.
4. Gavett BE, Poon SJ, Ozonoff A, Jefferson AL, Nair AK, Green RC, Stern RA. Diagnostic utility of the NAB List Learning test in Alzheimer’s disease and amnestic mild cognitive impairment. J Int Neuropsychol Soc 2009;15: 121-129.
5. Delis DC, Kramer, J. H., Kaplan, E., and Ober, B. A. The California Verbal Learning Test: Research Edition, Adult Version. 1987, San Antonio, TX. The Psychological Corporation.
6. Blacker D, Lee H, Muzikansky A, Martin EC, Tanzi R, McArdle JJ, Moss M, Albert M. Neuropsychological measures in normal individuals that predict subsequent cognitive decline. Arch Neurol 2007;64:862-871.
7. Rabin LA, Pare N, Saykin AJ, Brown MJ, Wishart HA, Flashman LA, Santulli RB. Differential memory test sensitivity for diagnosing amnestic mild cognitive impairment and predicting conversion to Alzheimer’s disease. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn 2009;16:357-376.
8. Woodard JL, Goldstein FC, Roberts VJ, McGuire C. Convergent and discriminant validity of the CVLT (dementia version). California Verbal Learning Test. J Clin Exp Neuropsychol 1999;21:553-558.
9. Kramer JH, Rosen HJ, Du AT, Schuff N, Hollnagel C,

Weiner MW, Miller BL, Delis DC. Dissociations in hippocampal and frontal contributions to episodic memory performance. Neuropsychology 2005; 19: 799-805.

10. Chang CC, Kramer JH, Lin KN, Chang WN, Wang YL, Huang CW, Lin YT, Chen C, Wang PN. Validating the Chinese version of the Verbal Learning Test for screening Alzheimer's disease. J Int Neuropsychol Soc 2010; 16: 244-251.
11. Steffener J, Brickman AM, Rakitin BC, Gazes Y, Stern Y. The impact of age-related changes on working memory functional activity. Brain Imaging Behav 2009; 3: 142-153.
12. Brickman AM, Zimmerman ME, Paul RH, Grieve SM, Tate DF, Cohen RA, Williams LM, Clark CR, Gordon E. Regional white matter and neuropsychological functioning across the adult lifespan. Biol Psychiatry 2006; 60: 444-453.
13. Butters N, Granholm E, Salmon DP, Grant I, Wolfe J. Episodic and semantic memory: a comparison of amnesic and demented patients. J Clin Exp Neuropsychol 1987; 9: 479-497.
14. Sarazin M, Berr C, De Rotrou J, Fabrigoule C, Pasquier F, Legrain S, Michel B, Puel M, Volteau M, Touchon J, Verny M, Dubois B. Amnestic syndrome of the medial temporal type identifies prodromal AD: a longitudinal study. Neurology 2007; 69: 1859-1867.
15. Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Ritchie K, Rossor M, Thal L, Winblad B. Current concepts in mild cognitive impairment. Arch Neurol 2001; 58: 1985-1992.
16. Artero S, Petersen R, Touchon J, Ritchie K. Revised criteria for mild cognitive impairment: validation within a longitudinal population study. Dement Geriatr Cogn Disord 2006; 22: 465-470.
17. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189-198.
18. Liu HC, Teng EL, Lin KN, Hsu TC, Guo NW, Chou P, Hu HH, Cheng WN, Chiang BN. Performance on a dementia screening test in relation to demographic variables. Study of 5297 community residents in Taiwan. Arch Neurol 1994; 51: 910-915.
19. Warschausky S, Kay JB, Chi P, Donders J. Hierarchical linear modeling of California Verbal Learning Test-Children's Version learning curve characteristics following childhood traumatic head injury. Neuropsychology 2005; 19: 193-198.
20. Welsh KA, Butters N, Hughes JP, Mohs RC, Heyman A. Detection and staging of dementia in Alzheimer's disease. Use of the neuropsychological measures developed for the Consortium to Establish a Registry for Alzheimer's Disease. Arch Neurol 1992; 49: 448-452.
21. Hudon C, Belleville S, Gauthier S. The association between depressive and cognitive symptoms in amnestic mild cognitive impairment. Int Psychogeriatr 2008; 20: 710-723.
22. Huh TJ, Kramer JH, Gazzaley A, Delis DC. Response bias and aging on a recognition memory task. J Int Neuropsychol Soc 2006; 12: 1-7.
23. Chow TW, Binns MA, Freedman M, Stuss DT, Ramirez J, Scott CJ, Black S. Overlap in frontotemporal atrophy between normal aging and patients with frontotemporal dementias. Alzheimer Dis Assoc Disord 2008; 22: 327-335.
24. Paul R, Grieve SM, Chaudary B, Gordon N, Lawrence J, Cooper N, Clark CR, Kukla M, Mulligan R, Gordon E. Relative contributions of the cerebellar vermis and prefrontal lobe volumes on cognitive function across the adult lifespan. Neurobiol Aging 2009; 30: 457-465.
25. Raine A, Lencz T, Reynolds GP, Harrison G, Sheard C, Medley I, Reynolds LM, Cooper JE. An evaluation of structural and functional prefrontal deficits in schizophrenia: MRI and neuropsychological measures. Psychiatry Res 1992; 45: 123-137.
26. Kim YT, Lee SW, Kwon DH, Seo JH, Ahn BC, Lee J. Dose-dependent frontal hypometabolism on FDG-PET in methamphetamine abusers. J Psychiatr Res 2009; 43: 1166-1170.
27. Tarnok Z, Barsi P, Gadoros J, Halasz P. [Executive dysfunction in frontal lesions and frontal epilepsy]. Ideggyogy Sz 2006; 59: 269-280.
28. Delis DC, Freeland J, Kramer JH, Kaplan E. Integrating clinical assessment with cognitive neuroscience: construct validation of the California Verbal Learning Test. J Consult Clin Psychol 1988; 56: 123-130.
29. Fuld PA, Katzman R, Davies P, Terry RD. Intrusions as a sign of Alzheimer dementia: chemical and pathological verification. Ann Neurol 1982; 11: 155-159.

30. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, Nordberg A, Backman L, Albert M, Almkvist O, Arai H, Basun H, Blennow K, de Leon M, DeCarli C, Erkinjuntti T, Giacobini E, Graff C, Hardy J, Jack C, Jorm A, Ritchie K, van Duijn C, Visser P, Petersen RC. Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med 2004; 256: 240-246.