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Journal
Neuropsychology, 28(2)

ISSN
0894-4105

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Publication Date
2014-03-01

DOI
10.1037/neu0000013

Peer reviewed

Published in final edited form as:
Neuropsychology. 2014 March ; 28(2): 273–280. doi:10.1037/neu0000013.

Memory consolidation in aging and MCI after 1 week

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Abstract

Objective—To assess consolidation in amnestic mild cognitive (aMCI) impairment, controlling for differences in initial learning and using a protracted delay period for recall.

Methods—Fifteen individuals with MCI were compared to fifteen healthy older adult controls on a story learning task. Subjects were trained to criteria to equalize initial learning across subjects. Recall was tested at both the 30-minute typically used delay and a 1-week delay used to target consolidation.

Results—Using repeated measures ANOVAs adjusted for age, we found group × time point interactions across the entire task between the final trial and 30-minute delay, and again between the 30-minute and 1-week delay periods, with MCI having greater declines in recall as compared to controls. Significant group main effects were also found, with MCI recalling less than controls.

Conclusion—Consolidation was impaired in aMCI as compared to controls. Our findings indicate that MCI-related performance typically measured at 30 minutes underestimates MCI-associated memory deficits. This is the first study to isolate consolidation by controlling for initial learning differences and using a protracted delay period to target consolidation in an MCI sample.

Keywords

consolidation; episodic learning; amnestic mild cognitive impairment; memory; cognitive aging

Introduction

Considered a prodrome of Alzheimer's disease (AD), amnestic mild cognitive impairment (aMCI) is a diagnosis given to non-demented individuals with progressive memory decline. The earliest affected brain region in aMCI is the medial temporal lobe (Convit et al., 1997; Dickerson & Sperling, 2008; Korf, Wahlund, Visser, & Scheltens, 2004; Pennanen et al., 2005; Pihlajamaki, Jauhiainen, & Soininen, 2009), a region thought to support memory consolidation (Alvarez & Squire, 1994; Maguire, Henson, Mummery, & Frith, 2001; Niki & Luo, 2002; Piefke, Weiss, Zilles, Markowitsch, & Fink, 2003; Tsukiura et al., 2002).

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C M Walsh (corresponding author) did the statistical analyses.

Therefore it stands to reason that consolidation itself should be impaired in aMCI. Though there has been extensive research on memory recall and forgetting in aMCI, this has typically been limited to a 20 to 30-minute delay, missing much of the consolidation period. Patients with aMCI also have deficits in immediate recall (Greenaway et al., 2006; Moulin, James, Freeman, & Jones, 2004; Rabin et al., 2009; Ribeiro, Guerreiro, & De Mendonca, 2007; Silva et al., 2012), which introduces potential bias when attempting to study retention over delays.

There has been some debate whether increased forgetting rates in AD and aMCI may be a function of impaired learning with intact consolidation (Mayes, 1986), resulting in normal rates of forgetting once information is learned (Becker, Boller, Saxton, & McGonigle-Gibson, 1987; Christensen, Kopelman, Stanhope, Lorentz, & Owen, 1998; Degenszajn, Caramelli, Caixeta, & Nitrini, 2001; Freed, Corkin, & Cohen, 1987; Kopelman, 1985). Alternatively, as we hypothesize individuals with aMCI or AD have an increased rate of forgetting (Budson et al., 2007; Christensen et al., 1998; Greenaway et al., 2006; Kramer et al., 2004; Larrabee, Youngjohn, Sudilovsky, & Crook, 1993; Manes, Serrano, Calcagno, Cardozo, & Hodges, 2008; McBride et al., 2002; Reed, Paller, & Mungas, 1998), even when initial encoding is controlled for (Christensen et al., 1998; Hart, Kwentus, Harkins, & Taylor, 1988; Larrabee et al., 1993). The variability in forgetting rates may depend on the information itself being assessed (Christensen et al., 1998). Increased forgetting may occur only within the first 10 minutes following learning (Giambra & Arenberg, 1993) or may persist for months (Budson et al., 2007), suggestive of impaired consolidation. As previously suggested, it is likely that impairments in consolidation or the increased rate of forgetting are a feature of AD pathology independent of initial encoding deficits (Moulin et al., 2004).

Few have controlled for initial differences in learning or encoding, making it difficult to assess comparative rates of forgetting. The goal of this study was to investigate the effect of aMCI on consolidation using i) a paradigm that matches groups on initial acquisition of information, and ii) delay periods that more comprehensively cover the consolidation period. We hypothesized that when controlling for potential initial differences in immediate recall, aMCI would demonstrate impaired delayed recall after 30 minutes and after a 1-week delay.

Methods

Participants

Subjects were 35 community-dwelling individuals over the age of 60 recruited through the University of California, San Francisco (UCSF) Memory and Aging Center's longitudinal observational studies. All participants received comprehensive evaluations including a neurological exam, neuropsychological assessment, and an informant interview. Participants were screened for a variety of disorders including history of clinically significant stroke, traumatic brain injury, psychiatric disorder and reversible causes of cognitive decline. Consensus diagnoses were made by a team of neurologists, nurses, neuropsychologists, and trained support staff. Participants were enrolled if they had a diagnosis of either aMCI (MCI) or were clinically healthy (control). Normal control participants (HC) were recruited from the UCSF Hillblom Healthy Aging Cohort (Hillblom Foundation Network Grant) who

had no evidence of a neurodegenerative disease, epilepsy, active neoplastic disease or substance abuse. Healthy controls for this study were defined as subjects with a clinical dementia rating score (CDR) of 0, with no significant history of cognitive complaints and normal cognitive testing. All aMCI subjects were diagnosed with MCI through the UCSF Memory and Aging Center and were co-enrolled in both the Alzheimer's Disease Research Center at UCSF and the "Predictors of Cognitive Decline" (PCD) study at the San Francisco VA Medical Center. An aMCI diagnosis was made if 2 of the following criteria were met: 1) self-complaint of memory impairment, 2) CDR of 0.5 for memory provided by a reliable informant, 3) impaired performance on standard memory testing (below 1 standard deviation of the mean), and/or 4) physician concern about underlying Alzheimer's disease.

Two individuals (1 = MCI, 1 = HC) were excluded because they could not be contacted within the specified time frame for the 1-week delay interval and three (2 = MCI, 1= HC) could not learn the story to the specified 90% criteria. The final sample was 15 controls (5 men, 70.5 ± 4 years) and 15 aMCI (7 men, 74.8 ± 7 years). As part of their enrollment in other studies, all subjects were administered the 30-item Geriatric Depression Scale (GDS), Mini Mental State Exam (MMSE), and California Verbal Learning Test (Delis, Freeland, Kramer, & Kaplan, 1988). CVLT-II data for one subject in the MCI sample was invalid and not included in these results. This study was approved by the UCSF Institutional Review Board (IRB). All participants gave written informed consent prior to starting this study.

Assessment of Recall: Story Learning Task

Using a 20-unit story learning task (Butler et al., 2009; Lezak, 1995), subjects were read the story a minimum of five times and asked to immediately recall it after each reading. Training on the story continued until the subject reached a learning criterion of 90% (see Table 1). Subjects were asked to recall the story at 30-minute and 1-week delays. The 1-week recall was attained by telephone follow-up and was used to specifically address consolidation. During this telephone follow-up, participants were asked to re-tell the story to the examiner. Participants were not told at the time of original testing that they would be asked to recall the story at the one-week time point, only that they would be contacted.

Statistics

Independent t-tests were used to determine group differences for age, GDS, MMSE, education, number of learning trials for the story task, and the number of days to follow up. Repeated measures ANOVAs (RMANOVA) were used to determine testing time × group interactions for percent recall adjusting for age. When violations of sphericity were encountered, we used the Greenhouse-Geisser correction. We further explored the rates of forgetting to provide additional support for the amount of forgetting observed. We did this by calculating each subject's slope of the linear regression between data points for i) the final-trial and 30-minute recall (initial rate of forgetting), and ii) the 30-minute recall and 1-week recall (later rate of forgetting). Each subject's line slopes were then analyzed using both paired t-tests and ANCOVA adjusting for age. Additional analyses were performed using the number of trials to reach criteria as an additional covariate to determine if differences in acquisition contributed to our findings. Data are presented as mean and standard deviations except where noted.

Results

Characteristics of Study Sample

The MCI sample in our study was marginally older (74.8 ± 7 years) than our healthy control group (70.5 ± 4 years; t = 2.091, p = 0.048). As expected, the MMSE was lower in the aMCI (28.4 ± 1.4) group than controls (29.5 ± 0.8; t = 2.76, p = 0.01) and the aMCI group performed worse than controls on a clinical memory test (CVLT-II delayed recall, t = 3.03, p = 0.007). Education (t = 0.23, p = 0.82) and GDS (t = 0.98, p = 0.34) did not differ between the two groups. See Table 2 for details.

Recall at Both 30 Minutes and 1 Week After Learning to Threshold

There was a group difference for the number of trials to reach threshold (t = 2.13, p = 0.05) (see Table 1). As expected given the requirements of the paradigm, immediate recall at the end of the story-learning session was equivalent between groups (t = 1.59, p = 0.12).

Adjusted RMANOVA across the three time points (final learning trial, 30-minute recall and 1-week recall) indicated a time × group interaction (F(1.31,27) = 11.62, MSE = 0.195, η_p^2 = 0.301, p = 0.001; see Figure 1). Follow-up analyses investigated the interaction between performance on the final training trial and 30-minute recall, as well as between both the 30-minute and 1-week delayed recall sessions. There was a significant time × group interaction between recall on the final training trial and 30-min recall (adjusted RMANOVA, F(1,27) = 5.72, MSE = 0.017, η_p^2 = 0.175, p = 0.02). Similarly, the time × group interaction between the 30-minute and 1-week testing sessions was also significant (adjusted RMANOVA, F(1,27) = 8.85, MSE = 0.127, η_p^2 = 0.247, p = 0.006). Across the three time points, there was also a significant main effect for diagnosis, with MCI subjects performing worse than controls (adjusted RMANOVA, F(1,29) = 22.97, MSE = 0.385, η_p^2 = 0.46, p<0.001) but there was no significant time main effect (adjusted RMANOVA, F(1.31, 27) = 1.1, MSE = 0.018, η_p^2 = 0.039, p = 0.32).

All subjects received a minimum of 5 acquisition trials, however some subjects learned the task in fewer trials, therefore we investigated whether the number of trials to reach criteria may have contributed to our findings. To determine this, we performed a RMANOVA across the two periods (30-minute recall and 1-week recall) adjusting for both age and the number of trials to reach criteria. Overall, adjusting for the number of trials to reach criteria had little effect on our previous findings, retaining the time × group interaction (F(1,26) = 10.32, MSE = 0.144, η_p^2 = 0.284, p = 0.003).

To further assess rates of forgetting, we used ANCOVA (adjusting for age) and paired t-tests to investigate if there were differences in the slopes between performance on a) the initial rate of forgetting (final trial and 30-minute recall) and b) later rate of forgetting (30-minute recall and 1-week recall). Using paired t-tests, both the MCI (t = 3.817, p = 0.002) and control (t = 6.016, p < 0.001) groups had greater rates of forgetting on the later forgetting phase. MCI had increased rates of forgetting on both the initial (F(1,27) = 5.72, MSE = 0.035, η_p^2 = 0.175, p = 0.024) and later (F(1,27) = 8.85, MSE = 0.255, η_p^2 = 0.247, p = 0.006) forgetting phases as compared to controls. However, when the number of training trials to reach criteria was used as a covariate, there was a significant rate of forgetting phase

× group interaction ($F(1,26) = 4.74$, MSE = 0.088, $\eta_p^2 = 0.154$, $p = 0.039$). When we controlled for the number of trials to reach criteria, MCI no longer had a greater initial rate of forgetting ($F(1,26) = 2.2$, MSE = 0.014, $\eta_p^2 = 0.078$, $p = 0.15$). This suggests that initial rate of forgetting is affected by the number of trials to reach criteria. Overall there was little effect of the number of trials to reach criteria on the later rate of forgetting, with MCI still having a greater rate of forgetting than controls ($F(1,26) = 10.32$, MSE = 0.287, $\eta_p^2 = 0.284$, $p = 0.003$).

Discussion

Our main finding is that patients with aMCI show evidence for impaired delayed recall even when groups are carefully matched on initial learning. With equivalent initial learning, aMCI subjects forgot more information across recall trials than controls, indicating an underlying deficit in memory consolidation. Compared to controls, aMCI subjects had an increased rate of forgetting within the first 30-minutes, and more importantly a greater rate of forgetting was evident between the 30-minute and 1-week recall sessions even when the number of trials to reach criteria was controlled for. Therefore rates of forgetting are increased in individuals with MCI, which lasts for multiple days, independent of acquisition deficits. This indicates that the shorter (20-30 minutes) delay periods typically used in clinical and research assessments under represent aMCI-related deficits by only sampling a narrow range of the consolidation period.

Several previous reports have described MCI-associated impairments in immediate recall (Greenaway et al., 2006; Moulin et al., 2004; Rabin et al., 2009; Ribeiro et al., 2007; Silva et al., 2012), delayed recall (20-30 minutes, (Belleville, Sylvain-Roy, de Boysson, & Menard, 2008; Della Sala, Cowan, Beschin, & Perini, 2005; Hudon et al., 2006; Rabin et al., 2009; Tremont, Miele, Smith, & Westervelt, 2010) and autobiographical longer term memory (Leyhe, Muller, Milian, Eschweiler, & Saur, 2009), but none have directly addressed consolidation. Consolidation is an active reorganization of the memory process, involving the strengthening of synaptic connections and the recruitment of additional brain areas which will later improve recall (Milner, 1989; Paller, 1997; Squire & Alvarez, 1995; Teyler & DiScenna, 1986; Wittenberg & Tsien, 2002). The process of consolidation is mediated by the medial temporal cortex, an area known to be negatively affected early in AD (Kramer & Miller, 2000) and aMCI (Dudai, 2004; Manes et al., 2008; Masdeu, Zubieta, & Arbizu, 2005; Squire & Alvarez, 1995). Atrophy within the medial temporal lobe (with entorhinal cortex) in MCI is associated with rapid forgetting (within 30 minutes) of a learned story (Shimada et al., 2012). How long the medial temporal lobe remains involved in the memory consolidation and retrieval process remains a point of debate. Memories may be dependent on the medial temporal lobe for the initial consolidation period only (Alvarez & Squire, 1994; Bayley, Hopkins, & Squire, 2003) or for life (Moscovitch & Nadel, 1998; Nadel & Moscovitch, 1997; Ryan et al., 2001; Westmacott, Leach, Freedman, & Moscovitch, 2001).

Mechanistically, successful memory storage is thought to rely on two consolidation stages: synaptic consolidation and system consolidation. Synaptic consolidation involves synaptic plasticity, a set of molecular and cellular processes that occurs within the medial temporal lobe on the minutes to hours' timeframe. Much of the research on synaptic plasticity and

memory supports this theory utilizing both in vitro (Deisseroth, Bito, & Tsien, 1996; Frank & Greenberg, 1994; Frey, Krug, Reymann, & Matthies, 1988; Klein et al., 2002) and in vivo animal research (Abel et al., 1997; Grecksch & Matthies, 1980; Meiri & Rosenblum, 1998; Yin et al., 1994). In contrast, system consolidation, which also involves the medial temporal lobe, is thought to occur on a timeframe ranging from days to possibly years recruiting additional brain regions to store the memory. The system consolidation theory is supported by in vivo animal (Alvarez & Squire, 1994; Bontempi, Laurent-Demir, Destrade, & Jaffard, 1999; Cho, Beracochea, & Jaffard, 1993; Kim & Fanselow, 1992; Winocur, 1990; Zola-Morgan & Squire, 1990) and human research (Bayley et al., 2003; Haist, Bowden Gore, & Mao, 2001; Scoville & Milner, 1957), with many indicating that a memory is never independent of the medial temporal lobe (Moscovitch & Nadel, 1998; Nadel & Moscovitch, 1997; Ryan et al., 2001; Westmacott et al., 2001). Both synaptic and system consolidation are thought to be affected in aMCI. Amyloid-beta, a protein associated with the development of AD and measurable in aMCI, has been shown to disrupt synaptic plasticity using in vitro (Balietti et al., 2012; Dickey et al., 2004; Puzzo et al., 2005) and in vivo animal research (Borlikova et al., 2013; Freir et al., 2011), thereby impacting synaptic consolidation. Consolidation may also be impaired in aMCI resulting from disrupted networks connecting the medial temporal lobe to cortical areas involved in system consolidation. Specifically, previous in vivo human research has described disrupted functional connectivity between the hippocampus and the prefrontal, temporal and parietal cortices in MCI as compared to healthy controls (Bai et al., 2009; Bokde et al., 2006; Protzner, Mandzia, Black, & McAndrews, 2011; Wang et al., 2006; Wang et al., 2007; Yao et al., 2010; Zhou et al., 2008) which was associated with impaired memory performance (Bai et al., 2009; Protzner et al., 2011; Wang et al., 2006). Though the 30-minute delayed recall period is typically thought to reflect longer-term memory, the process of synaptic consolidation itself is not yet complete at 30 minutes. Therefore the behavioral effect is not yet measureable at such a short delay window, and a longer delay similar to the 1-week delay used here may be necessary to describe aMCI-related consolidation deficits. Further research is warranted to determine if the impairments observed at 1 week in aMCI result from synaptic consolidation alone or reflect system consolidation deficits as well.

Though we are the first to combine a long delayed recall with initial equivalent learning, our study is not the first to test recall at a long delay in MCI (Manes et al., 2008). It was previously shown that both aMCI and individuals with self-reported mild memory complaints had increased forgetting observed at a 6-week recall which was not apparent earlier, in particular for those with self-reported mild memory complaints (Manes et al., 2008). Our results support these previous findings that recall at shorter delays can underestimate consolidation deficits. Practice effects are often reduced or absent in MCI compared to healthy controls (Cooper, Lacritz, Weiner, Rosenberg, & Cullum, 2004; Darby, Maruff, Collie, & McStephen, 2002; Duff et al., 2008; Duff et al., 2011; Galvin et al., 2005; Schrijnemaekers, de Jager, Hogervorst, & Budge, 2006). Our findings may suggest that a failure to consolidate could be the mechanism by which patients with MCI have decreased practice effects after 1 week or longer.

Learning to criteria to separate the effects of acquisition from recall has been studied in a range of neurological conditions including epilepsy (Muhlert et al., 2011; Wilkinson et al.,

2012), traumatic brain injury (Vanderploeg, Crowell, & Curtiss, 2001) and multiple sclerosis (Gaudino, Chiaravalloti, DeLuca, & Diamond, 2001). In individuals with temporal lobe epilepsy (TLE) as compared to individuals with idiopathic generalized epilepsy with equivalent acquisition performance, recall was impaired at 30 minutes and 3 weeks (Muhlert et al., 2011). Based on findings in individuals with TLE, it is possible that recall at both the i) minutes-to-hours delay and ii) weeks delay rely on different hippocampal sub-regions (Wilkinson et al., 2012). Not all of the neurological disorders groups showed increased forgetting tested after a week or more delay. Together with our results, this could suggest increased sensitivity to impairments using very-long delayed recall, and a vulnerability in aMCI (Gaudino et al., 2001; Muhlert et al., 2011; Vanderploeg et al., 2001; Wilkinson et al., 2012).

It should be noted that the MCI sample in our study might not have been as impaired as those in other studies. Our definition of an individual with amnestic MCI differed from that described in both the International Consensus Panel's (Winblad et al., 2004) and Petersen's (Petersen, 2004) criteria. Similar to our study, both the International Consensus and Petersen criteria require an individual to not have normal cognition, not be demented and have mostly intact activities of daily living. An aMCI diagnosis by the International consensus panel also requires either a decline in cognitive testing, or both a memory impairment on cognitive testing and either a self-reported or informant-reported decline in cognition. The Petersen criteria also require that an individual with aMCI must have a self-reported cognitive decline, a memory impairment on cognitive testing, and preserved general cognitive function. In comparison, our criteria lower the weight on impaired cognitive testing in the memory domain and heighten the informant and self-reported memory complaints. Individuals in our aMCI group may not be as impaired on cognitive testing (e.g. MMSE and CVLT-II recall). Our small sample of subjects is from a geographically constricted area with relatively high levels of education and high MMSE scores. Therefore, it is possible that our aMCI subjects were less impaired than those used in other studies and may not be representative of the population at large. Even with a potentially more intact, relatively high functioning group of aMCI subjects, our study still showed consolidation deficits and increased rates of forgetting as compared to healthy controls.

As hypothesized, aMCI subjects showed greater loss of information over 1 week than controls, even when controlling for initial learning. These findings suggest that delayed recall deficits in aMCI are likely due to impaired consolidation rather than deficits in initial learning. They also suggest that the standard 20-30 minute delays in most extant memory paradigms may underestimate the degree to which memory is impaired in aMCI, and that clinicians might need longer delay periods to elicit deficits in very mildly impaired patients. Currently there is a need for more sensitive measures to subtle changes in MCI. This study highlights a modified way of assessing memory declines in individuals with aMCI, which may not be otherwise detected in a clinical setting. Though many individuals in the MCI sample reported memory declines and were not pre-symptomatic, many did not have measurable impairments on traditional neuropsychological testing. Our study highlights the need for consolidation-specific cognitive tests that are sensitive to subtle impairments, necessary for both early diagnosis and to differentiate memory change in clinical trials.

Acknowledgments

Funding sources: AG010897 (PCD), P50AG023501 (ADRC), AG032289 (Kramer) and Hillblom Foundation Network Grant. We would like to acknowledge Dr. Michael W Weiner and Dr. Linda L Chao for their contributions to this study.

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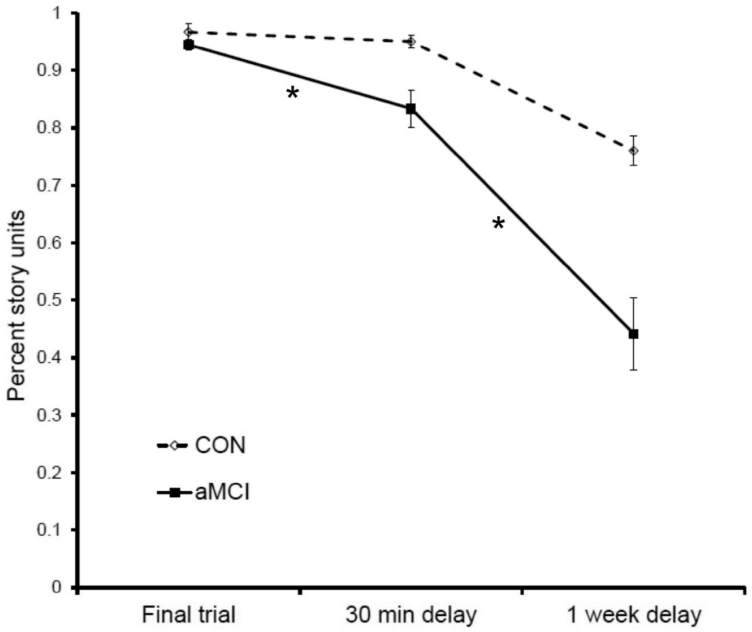

Figure 1. Story recall in aMCI and healthy aged controls

Subjects were trained to 90% threshold on a story learning task. In a comparison of each subject's final learning score (Final Trial), there were no group differences. We identified a significant group × time interaction between the final trial and 30-min delay (*, $p < 0.05$), and again between the 30-minute delay and 1-week delay (*, $p < 0.05$). aMCI (solid line) performed worse than controls (dashed line). Data are presented as mean ± SEM of the percent of story units recalled.

Table 1

Learning across training trials

Training across trials is shown for each group. The number of individuals within each group (n) is indicated per trial. Median percent correct (Med) is shown for each trial. The number of individuals (n) within each group to get 100% correct out of the total sample tested (denominator) on the training trial is indicated. After Trial 5, no control subject needed additional trials, therefore Trials 6 to 9 do not have data for the healthy controls (HC).

	Trial 1		**Trial 2**		**Trial 3**		**Trial 4**		**Trial 5**		**Trial 6**		**Trial 7**		**Trial 8**		**Trial 9**	
	Med	n	Med	n	Med	n	Med	n	Med	n	Med	n	Med	n	Med	n	Med	n
HC	0.6	0/15	0.9	2/15	0.95	6/15	1	8/15	1	10/15	-	-	-	-	-	-	-	-
MCI	0.45	0/15	0.7	0/15	0.75	1/15	0.9	2/15	0.95	2/15	0.85	0/5	0.875	0/4	0.9	0/2	0.9	0/1

Table 2

Group characteristics

Number of learning trials indicates the number of trials during story learning to reach criteria. Number of days indicates the delay period between learning the story to threshold and the 1-week delayed recall. Sample size is shown as count. All other data are presented as mean ± standard deviation and analyzed using independent *t*-tests.

Group	Control	aMCI	p-value
N (males)	15 (5)	15 (7)	
Age (years)	70.5 ± 4	74.8 ± 7	0.05*
Education (years)	17.6 ± 2	17.4 ± 3	0.82
GDS (max = 30)	2.9 ± 4	4.5 ± 5	0.34
MMSE (max = 30)	29.5 ± 1	28.4 ± 1	0.01*
CVLT-II Long free recall (max = 16)	13.5 ± 2	9.7 ± 4	< 0.01*
Number of learning trials	5.0 ± 0	5.7 ± 1	0.05*
Number of days	7.3 ± 1	7.9 ± 2	0.25