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Retrograde Memory for Public Events in Mild Cognitive Impairment and Its Relationship to Anterograde Memory and Neuroanatomy

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(for the Alzheimer's Disease Neuroimaging Initiative)

Objective: The study characterized the status of retrograde amnesia (RA) in amnestic mild cognitive impairment (MCI). ***Method:*** We measured RA, anterograde amnesia (AA), brain measures, apolipoprotein-E status (ApoE), and conversion to probable Alzheimer's disease (AD) across 3 years in 15 individuals with MCI. We compared the severity of amnesia and brain atrophy in MCI to a group of patients with limited damage to the hippocampus (H) or more extensive damage to the medial temporal lobe (MTL). ***Results:*** The MCI group exhibited modest AA, together with severe RA, covering nearly 4 decades before their diagnosis. Compared with H-MTL patients, the temporal extent of RA was disproportionate to the severity of AA. The MCI group exhibited more modest AA and MTL atrophy than H-MTL patients, together with more severe RA and neocortical atrophy than H-MTL patients. The severity of AA corresponded to the integrity of MTL structures, whereas the severity of RA corresponded to the integrity of both MTL and neocortical structures. RA (but not AA, nor measures of cognitive status) was related to ApoE status and subsequent diagnosis of probable AD. RA was predicted by heritable risk for AD, in addition to the integrity of MTL and neocortical structures. ***Conclusions:*** Compared with H-MTL patients, the MCI group exhibited RA that was disproportionate to their AA and that was more severe than would be expected if their atrophy were limited primarily to the MTL. Heritable risk for AD, as well as the integrity of brain regions within and beyond the MTL, are important for understanding RA in MCI.

Keywords: semantic memory, mild cognitive impairment, retrograde amnesia, anterograde amnesia

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Mild cognitive impairment (MCI) is considered a transitional stage between healthy aging and Alzheimer's disease (AD; Petersen et al., 1999), and individuals with MCI are at an increased risk of developing AD (at a rate of 16% per year; Petersen et al., 2005). Amnestic MCI is associated with cognitive impairment limited to the domain of memory. These individuals exhibit anterograde memory impairment (difficulty learning new information) that is often intermediate in severity between normal controls and AD (Ally, Gold, & Budson, 2009; Petersen et al., 1999). The severity of anterograde memory

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deficits in both MCI and AD are related to the integrity of structures in the medial temporal lobe (MTL), specifically the hippocampus (H) and entorhinal cortex (Sexton et al., 2010; Walhovd et al., 2010).

MTL damage is also associated with retrograde amnesia, that is, difficulty remembering information acquired prior to the onset of amnesia (Bayley, Hopkins, & Squire, 2006; Smith, Frascino, Hopkins, & Squire, 2013). The status of retrograde amnesia in MCI has received relatively little attention, and the available studies have yielded mixed findings. Retrograde amnesia has been described as absent (for nonautobiographical memory, Thomann et al., 2012), mild and temporally limited (for autobiographical memory, Irish, Lawlor, O'Mara, & Coen, 2009; Leyhe, Muller, Milian, Eschweiler, & Saur, 2009; Murphy, Troyer, Levine, & Moscovitch, 2008; Thomann et al., 2012), or severe and encompassing all time periods tested (Barbeau et al., 2012; Flicker, Ferris, Crook, & Bartus, 1987; Leyhe, Muller, Eschweiler, & Saur, 2010; Seidenberg et al., 2009). When overall performance on retrograde memory tests was examined (instead of the temporal extent of the impairment), impairment was consistently observed in MCI (Bizzozero, Lucchelli, Saetti, & Spinnler, 2012; Gardini et al., 2013; Joubert et al., 2008).

The status of retrograde amnesia is clearer in AD. This group exhibits severe retrograde amnesia that frequently encompasses the entire life span prior to the onset of amnesia (see Meeter, Eijsackers, & Mulder, 2006, for a review of seven AD studies). Yet atrophy in AD (though it begins in the MTL) eventually involves temporal, frontal, and parietal cortex (Braak & Braak, 1997; Dickerson et al., 2009; Thal, Rub, Orantes, & Braak, 2002; Thompson et al., 2003). Accordingly, the severity of retrograde amnesia in AD likely reflects atrophy not only of the MTL but also in the neocortex, most likely association cortices, where long-term memories are thought to be stored (Bayley, Gold, Hopkins, & Squire, 2005; Bright et al., 2006; Gilboa et al., 2005) or atrophy of the frontal lobe given its role in memory retrieval (Bayley et al., 2005; Kopelman, 1991; Kopelman et al., 2003; Kopelman, Stanhope, & Kingsley, 1999; Kroll, Markowitsch, Knight, & von Cramon, 1997). Notably, like AD patients, individuals with MCI also exhibit variable neuroanatomical changes outside the MTL (Bakkour, Morris, & Dickerson, 2009; Fennema-Notestine et al., 2009; McDonald et al., 2009; McEvoy et al., 2009; Whitwell et al., 2007). The severity of retrograde amnesia in MCI may therefore depend on the extent of anatomical changes outside the MTL. Neuroanatomical information, in conjunction with comprehensive neuropsychological testing, should clarify the status of retrograde amnesia in MCI.

One approach to the assessment of retrograde amnesia in MCI is to consider their scores compared with other memory-impaired patient groups in which neuroanatomical information is available. For example, memory-impaired patients with acute damage limited to the hippocampus (H patients), or with larger lesions of the MTL (hippocampus and parahippocampal gyrus), exhibited an orderly relationship between the extent of MTL damage, the severity of anterograde amnesia, and the severity of retrograde amnesia (Smith et al., 2013). Specifically, when damage was limited to the hippocampus, anterograde amnesia was moderately severe, and retrograde amnesia was limited to several years before the onset of amnesia. In contrast, larger lesions of the MTL produced more severe anterograde amnesia, and retrograde amnesia extended back several decades before the onset of amnesia. In H and MTL patients, there was a strong relationship between the severity of anterograde amnesia and the extent of retrograde amnesia ($r = .81$, $p < .05$). Given these findings, one can ask whether the relationship between anterograde and retrograde amnesia in MCI is the same or different than in H and MTL patients. For example, if individuals with MCI have anterograde and retrograde memory scores that deviate substantially from the relationship observed in H and MTL patients, then one might expect atrophic changes to have occurred outside of or in addition to the MTL.

We assessed anterograde memory and retrograde memory (i.e., memory for public events) in 15 individuals with amnestic MCI and 21 healthy controls (Experiment 1). The relationship between anterograde and retrograde memory impairment was evaluated in MCI and then compared with the scores on the same tests for 11 H and MTL patients (Experiment 2), as recently described (Smith et al., 2013). The behavioral performance of the MCI group on these tests generated three predictions regarding the severity of atrophic changes in particular brain regions. These predictions were then tested using structural brain measures of the MTL and neocortex in 11 of the individuals with MCI and 11 controls (Experiment 3).

Experiment 1: Anterograde and Retrograde Memory in MCI

Method

Participants. The participants were 15 individuals diagnosed with amnestic MCI (see Table 1). The individuals were diagnosed and referred by the Alzheimer's Disease Research Center (ADRC) at the University of California San Diego (UCSD) according to criteria proposed by Petersen and colleagues (Petersen et al., 2001). The criteria were memory complaints, impaired memory on psychometric testing, essentially normal activities of daily living, and otherwise normal general cognitive function. The individuals were diagnosed by consensus conference with neurologists, neuropsychologists, and staff that used all available clinical information, including psychometric test scores, standardized rating scales, and informant interviews. Individuals with MCI had no other significant neurologic illness, such as stroke. Individuals with amnestic MCI were referred to the study from the ADRC if they met three requirements: (a) indication of interest in participating in research, (b) an ability to speak and understand English, and (c) residence in the United States for most of his or her adult life. The latter two criteria were used because the measure of retrograde amnesia (see Measuring retrograde memory for news events) is in English, and a portion of the test items query events that may not be well known outside of the United States.

Twenty-one healthy volunteers recruited from the San Diego community served as controls for the MCI group (see Table 1). One to two controls were selected to match each member of the MCI group according to sex, age, and education. Controls had no significant neurologic illness or memory complaints. In addition, they exhibited no cognitive impairments (e.g., they performed within the normal range on the Information and Vocabulary subtests of the Wechsler Adult Intelligence Scale and within the normal range on a test of delayed prose recall [a test similar to the Wechsler Memory Scale–Revised (WMS-R) Logical Memory

Table 1
Experiment 1: Characteristics of MCI and Control Groups

Variables	Control group	MCI group				
			Effect size	ApoE risk	ApoE no risk	Effect size
Number of participants	21	15	—	7	8	—
Sex (male/female)	12/9	10/5	—	2/5	8/0	—
Age (years)	76.3 ± 1.6 (65–89)	78.7 ± 1.5 (66–87)	−0.3	78.8 ± 1.7 (71–86)	78.5 ± 2.6 (66–87)	−0.1
Education (years)	15.3 ± 0.7 (12–21)	15.3 ± 0.7 (12–20)	0.0	15.4 ± 1.1 (12–19)	15.1 ± 1.0 (12–20)	−0.3
Cognitive status						
MMSE		27.8 ± 0.5 (25–30)	—	27.7 ± 0.8 (25–30)	27.9 ± 0.6 (26–30)	0.1
CDR global score		0.5, n = 13; 1.0, n = 2	—	0.5, n = 6; 1.0, n = 1	0.5, n = 7; 1.0, n = 1	—
CDR Sum-of-Boxes		2.5 ± 0.3 (0.5–5)	—	2.9 ± 0.5 (2–5)	2.3 ± 0.5 (0.5–4)	0.6
CDR Subscales						
Memory		0.80 ± 0.07 (0.5–1)	—	0.79 ± 0.10 (0.5–1)	0.81 ± 0.09 (0.5–1)	0.0
Orientation		0.43 ± 0.14 (0–2)	—	0.57 ± 0.25 (0–2)	0.31 ± 0.13 (0–1)	0.5
Judgment/Problem Solving		0.37 ± 0.08 (0–1)	—	0.50 ± 0.11 (0–1)	0.25 ± 0.09 (0–0.5)	0.9
Community Affairs		0.47 ± 0.09 (0–1)	—	0.50 ± 0.15 (0–1)	0.44 ± 0.11 (0–1)	0.2
Home/Hobbies		0.47 ± 0.09 (0–1)	—	0.50 ± 0.11 (0–1)	0.44 ± 0.15 (0–1)	0.3
Personal Care		0.00 ± 0.00 (0–0)	—	0.00 ± 0.00 (0–0)	0.00 ± 0.00 (0–0)	—
Retrograde memory						
Accuracy (percent correct)	39.7 ± 2.8 (10.0–60.0)	33.2 ± 4.1 (9.4–59.2)	**0.8***	17.7 ± 3.6 (9.0–33.0)	37.3 ± 5.3 (18.0–59.0)	**1.2***
Temporal Extent of Amnesia (years)	—	39.0 ± 5.4 (0–70)	—	50.0 ± 6.4 (25–70)	29.4 ± 7.0 (0–50)	**0.9***
Anterograde memory						
Number of participants	15	15	—	7	8	—
DRS: Memory Subscale	24.3 ± 0.2 (23–25)	21.1 ± 0.8 (15–25)	**1.3***	20.1 ± 1.2 (16–25)	22.0 ± 1.2 (15–25)	0.5
WMS-R Logical Memory	26.4 ± 1.9 (11–37)	9.5 ± 1.6 (9–25)	**2.5***	8.0 ± 2.7 (0–21)	10.9 ± 2.0 (2–19)	0.4
Rey-Osterrieth Complex Figure	17.7 ± 1.1 (12–24)	11.7 ± 1.4 (5–22)	**1.2***	9.9 ± 1.2 (6–15)	13.3 ± 2.4 (5–22)	0.7
Paired-Associate Learning	20.6 ± 1.5 (11–29)	10.9 ± 1.6 (0–21)	**1.6***	11.3 ± 2.3 (2–21)	10.5 ± 2.4 (0–18)	–0.1

Note. Data are the means ± standard error of the means (ranges). CDR ratings of 0.5 and 1 correspond to questionable and mild dementia, respectively. Cognitive status scores were not obtained for controls. Retrograde memory represents percent correct scores on the news events test for events that occurred prior to the onset of amnesia for individuals with MCI and for the same questions in healthy controls. Effect sizes for differences between groups are reported as Cohen's d and reflect the difference between the means, in standard deviations. MCI = Mild Cognitive Impairment; ApoE = apolipoprotein E; MMSE = Mini-Mental State Examination; CDR = Clinical Dementia Rating; DRS = Dementia Rating Scale; WMS-R = Wechsler Memory Scale-Revised. Significant effects are highlighted in bold text. $p < .05$.

Subtest]). Fifteen of these individuals were available for the anterograde memory tests (described in Measuring anterograde memory).

Measuring cognitive status and heritable risk for AD for the MCI group. Three standard indices of cognitive status were obtained for the MCI group: the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975; maximum score = 30; a score below 28 is considered impaired); the Clinical Dementia Rating (CDR; Morris, 1993; CDR scores of 0, 0.5, 1, 2, and 3 correspond to normal, questionable dementia, mild dementia, moderate dementia, and severe dementia, respectively); and the CDR Sum of Boxes and the scores for each of its six subscales: Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care (the score for each subscale ranges from 0 to 3; a lower score indicates less impairment). Two individuals with MCI obtained CDR global scores of 1.0. One individual transitioned from a score of 0.5 to 1.0 within the time frame of the study, and the other individual had normal general cognitive function outside of the realm of memory. Apolipoprotein E (ApoE) status was also obtained for the MCI group.

Measuring retrograde memory for news events. The test was constructed from a pool of 314 questions covering notable news events that occurred in a specific year between 1931 and 2005. Testing occurred between 2007 and 2010. The news events test was administered in a free recall format (e.g., "What caused a suspension bridge to collapse over the Narrows at Tacoma, Washington?" [1940]; "Who killed John Lennon?" [1980]; "Who is Elizabeth Smart?" [2003]; the year the event occurred was not provided). For each individual in the MCI group, the questions ranged from the time of onset of amnesia to the time when the individual was 15 years old (M = 242.1 ± 14.2 questions per individual). Earlier time periods were not queried, because adults are known to have limited knowledge of news events that occurred during childhood or early adolescence (Squire, 1974). The onset of amnesia was taken to be the year when the individual was diagnosed with MCI. Given that decline to a level of function consistent with MCI typically occurs within about 5 years (Acosta-Baena et al., 2011; Marquis et al., 2002), we presume that participants were healthy 5 years and longer prior to their diagnosis.

The percentage of questions answered correctly was calculated for each 5-year time interval—from the 5 years preceding the onset of amnesia to the time when each individual in the MCI group was 15 years old. For each individual in the MCI group, one or two controls were aligned in the same manner. The severity of retrograde amnesia was measured in two ways. First, for all participants, total accuracy was obtained by taking the mean of the mean percent correct scores across all time intervals queried. Second, for the MCI group, the temporal extent of amnesia (in years) was calculated as follows. Data

from all 21 controls were aligned to each individual relative to the year of onset of that individual's amnesia. The temporal extent of retrograde amnesia was defined as the number of 5-year time intervals in which the individual's score was below the corresponding score of the controls ($p < .05$, one-sample t test). A mean of 20.0 ± 5.0 questions were available for each 5-year time interval. For each individual with MCI, all the measures described (cognitive status, anterograde memory, and retrograde memory) were obtained within 5.0 ± 0.8 months of each other.

Measuring anterograde memory.

Anterograde memory for news events. Some of the news events questions covered events that occurred after the onset of amnesia, that is, these questions assessed anterograde memory. Nine of the 15 individuals with MCI had questions that covered anterograde memory. A mean of 79.3 ± 17.8 questions was available for these nine individuals (and for their controls). Anterograde amnesia for news events was calculated for each individual with MCI as the mean percent correct score for these news events questions. Because these scores were not available for all 15 individuals in the MCI group, the scores were used primarily to confirm the relationship between anterograde and retrograde amnesia for the MCI group that was observed when anterograde memory was assessed with more conventional memory tests (see Conventional tests of anterograde memory). Specifically, anterograde amnesia for news events was not used for computing the correlations with brain measures. Instead, correlations with brain measures were carried out using the memory tests described below, which were available for all individuals in the MCI group.

Conventional tests of anterograde memory.

Delayed recall of a complex figure. Participants copied a complex diagram (Rey-Osterrieth figure; Osterrieth, 1944) and then attempted to reproduce it from memory after a 10- to 15-min delay. The copy and the reproduction of the figure were each scored on a 36-point scale (Taylor, 1998).

Paired-associate learning. Participants completed three study-test trials with a list of 10 unrelated word pairs (Squire & Shimamura, 1986). To begin, the word pairs were displayed one at a time while the experimenter read each pair aloud. Immediately after all 10 pairs had been presented, participants were shown the first word from each pair and asked to recall the second word. This procedure was repeated two more times with the same pairs, but each time in a different order. The score was the total number of pairs recalled (maximum = 30).

Dementia Rating Scale. Participants were administered the Memory subscale from the Dementia Rating Scale (Mattis, 1976; maximum score = 25 points).

WMS-R Logical Memory Subtest. Recall was tested for two short prose passages, each consisting of 25 segments. The first passage was read aloud to the participant, followed by an immediate recall test. The second passage was then read aloud, also followed by an immediate recall test. Recall of both passages was then tested 30 min later. The score was the sum of segments recalled from both passages at the 30-min test.

Testing for the anterograde memory tests followed testing for the retrograde memory test. Six controls were unavailable for further testing after completing the retrograde memory test. Based on the performance of the 15 remaining controls, z scores were calculated for each individual with MCI for each of the four conventional anterograde memory tests. The four z scores were then averaged to create a measure of anterograde memory impairment for each individual with MCI.

Analysis plan. Comparisons between groups were carried out using between-subjects t tests. T tests with pooled variance are reported unless the standard deviation of one of the groups was more than two standard deviations of the other group. In that case, t tests with separate variance are reported. Arithmetic means and standard errors of the means are reported. The control group was matched to the MCI group according to sex, age, and education. Moreover, for the MCI group, neither age nor education was related to the severity of retrograde or anterograde amnesia. Specifically, age and education were unrelated to mean accuracy on the news events test ($r = .22$, $p > .43$, and $r = .05$, $p > .85$, respectively), to the temporal extent of retrograde amnesia ($r = .31$, $p > .20$, and $r = .41$, $p > .10$, respectively), or to mean z scores from the four anterograde memory tests ($r = -0.39$, $p > .15$, and $r = .02$, $p > .90$, respectively). Accordingly, age and education were not included as covariates in the between-groups tests. To determine whether there was significant impairment in the MCI group for the anterograde memory z scores, these scores were compared with zero using a one-sample t test. There was no correction for multiple comparisons.

Results

Anterograde and retrograde amnesia in MCI. Retrograde memory was severely impaired, covering news events that occurred up to 35 years before the onset of amnesia (see Figure 1).

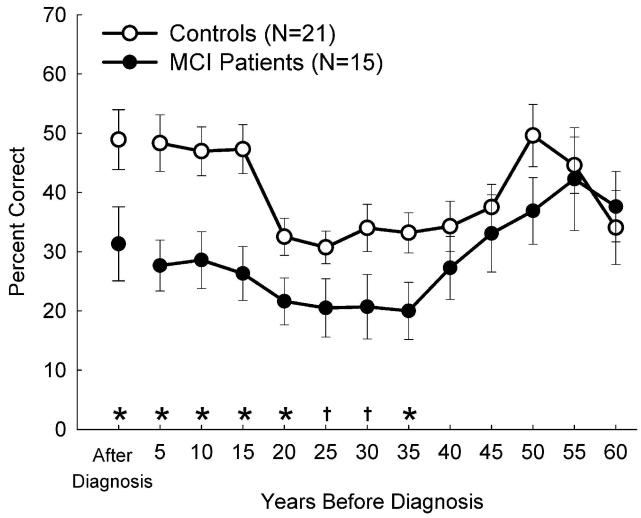

Figure 1. Experiment 1: Anterograde and retrograde (semantic) memory in mild cognitive impairment (MCI). Recall performance on a test of 314 news events that occurred from 1931 to 2005. The scores for each member of the MCI group, and one or two controls for each member, have been aligned relative to the year when that individual was diagnosed with amnestic MCI. The data point at 5 represents 1 to 5 years before diagnosis, the data point at 10 represents 6 to 10 years before diagnosis, and so on. The data point "After Diagnosis" represents the years after diagnosis (these scores are for nine of the 15 individuals with MCI). Differences in performance between MCI and controls are indicated by * $p < .05$ and † $p < .07$. Error bars indicate standard error of the mean.

Specifically, accuracy on the news events test for those seven 5-year time intervals was significantly poorer in the MCI group relative to controls, *t*s (34) = 2.2 to 3.4, *p*s < 0.05 to 0.005, except Time Interval 25, $t(34) = 1.9$, $p < .07$, and Time Interval 30, $t(34) = 2.0$, $p < .06$. (Note that the estimate of 35 years is approximate because, as indicated previously, there is a 5-year uncertainty about the time of onset of amnesia in individuals with MCI.) Despite the extent of retrograde memory impairment, the impairment was temporally limited. Scores for the MCI group were no different from controls for news events that occurred between 40 and 60 years before the onset of amnesia, and were virtually identical for the two most remote time intervals (55 and 60 years before onset). Specifically, the *t* tests comparing the MCI and control groups for the five most remote time periods were $t(34) = 1.0$, $p > .30$; $t(33) = 0.6$, $p > .5$; $t(33) = 1.6$, $p > .10$; $t(31) = 0.3$, $p > .80$; and $t(24) = -0.4$, $p > .60$, respectively. The MCI group also exhibited impaired anterograde memory for news events (Figure 1), $t(21) = 2.2$, $p < .05$. Likewise, for the four conventional tests of anterograde memory, impairment was observed for both verbal and pictorial material (see Table 1). Across these four memory tests, the mean *z* score for the MCI group was −2.5 ± 0.4 (and was significantly below zero, $t[14] = 5.8$, $p < .001$).

Relating anterograde and retrograde memory to heritable risk for AD and conversion to probable AD. Performance on the news events test was related to both ApoE status and to subsequent diagnosis of probable AD. First, the MCI group was divided into two groups depending on whether they had any heritable risk for developing AD (ApoE allele 4/4 and ApoE allele 3/4; $n = 7$) or no heritable risk of developing AD (ApoE allele 3/3 and ApoE allele 2/3; $n = 8$). Individuals with a heritable risk for AD performed more poorly on the news events test (i.e., average accuracy score taken across all 5-year periods prior to diagnosis) and exhibited a temporal extent of retrograde amnesia that was substantially longer compared with those with no heritable risk (see Table 1). By contrast, none of the measures of cognitive status or anterograde memory differed between these two groups (see Table 1). Moreover, there were also no differences between these two groups when anterograde memory was based on the *z* score derived from the four conventional measures, $t(13) = 1.1$, $p > .2$, nor when it was based on the news events test, $t(7) = 1.0$, $p > .3$.

Next, individuals with MCI were followed for 3 years after completing the news events test. Three individuals in the MCI group were diagnosed with probable AD within 3 years after completing the news events test, and nine continued to have a diagnosis of amnestic MCI (the remaining three participants were subsequently diagnosed with multiple-domain MCI or withdrew from follow-up visits). Compared with those who remained stable, the individuals who would be subsequently diagnosed with probable AD performed more poorly on the news events test (probable AD, 15.3 ± 2.7% correct; stable MCI, 30.6 ± 5.1% correct, $t[10] = 2.7$, $p < .05$) and exhibited a temporal extent of retrograde amnesia that was substantially longer (probable AD, 56.7 ± 4.5 years; stable MCI, 37.2 ± 7.3 years, $t[9.7] = 2.3$, $p < .05$). None of the other measures in Table 1, including the severity of anterograde amnesia, were related to a subsequent diagnosis of probable AD (MMSE, $t[10] = 0.2$, $p > .80$; CDR Global Score, $t[9.4] = 0.4$, $p > .6$; CDR subscales, *t*s [10] = −0.3 to 0.9, *p*s > 0.35 to 1.0; anterograde memory *z* score, $t[10] = -0.4$, $p > .70$). In summary, in the MCI group, retrograde amnesia provided the most sensitive measure for detecting heritable risk of AD and conversion to probable AD.

Experiment 2: Relating Anterograde and Retrograde Memory in MCI and MTL Amnesia

In Experiment 1, the MCI group exhibited very severe retrograde amnesia together with significant, but modest, anterograde amnesia. This finding was surprising because memory-impaired patients with retrograde amnesia as severe as the MCI group also normally exhibit very severe anterograde amnesia (Smith et al., 2013). Next, we directly compared the severity of anterograde amnesia and retrograde amnesia in the MCI group with a group of memory-impaired patients who have amnesia resulting from acute damage limited to the hippocampus (H patients) or larger lesions limited to the MTL (MTL patients).

Method

Participants. The MCI group ($N = 15$) and control group ($N = 21$) from Experiment 1 also participated in Experiment 2. In addition, 11 H and MTL patients served as a comparison group for the MCI group. The H and MTL patients (one female) averaged 56.5 ± 3.4 years of age and 13.0 ± 0.6 years of education. Additional information about this group appears elsewhere (Smith et al., 2013) and in Table S1 of the online supplemental materials. As a group, these patients were younger and less educated than the MCI group, $t(24) = 6.5$, $p < .001$, and $t(24) = 2.2$, $p < .05$, respectively. To calculate the severity of anterograde and retrograde amnesia in the H and MTL group, their scores were compared with a group of 42 healthy controls (as reported previously in Smith et al., 2013).

Measuring the severity of anterograde and retrograde amnesia. The scores from Experiment 1 for the severity of anterograde and retrograde amnesia for the MCI group were used for Experiment 2. Specifically, the severity of retrograde amnesia was the temporal extent of retrograde amnesia (in years), and the severity of anterograde amnesia was the mean *z* score based on the four conventional anterograde memory tests. The same measures were calculated for the H and MTL group. For the severity of retrograde amnesia, eight to 16 controls for each patient were identified from the 42 available controls, based on age, education, and when they took the news events test relative to the patient (within about one year). Some controls were matched to more than one patient. The severity of anterograde amnesia for the H and MTL group was calculated relative to 11 of the 42 controls who had scores for the four conventional anterograde memory tests.

Relating the severity of anterograde amnesia and retrograde amnesia. To measure the relationship between the severity of anterograde and retrograde amnesia, a correlation was computed between the anterograde amnesia *z* scores and the temporal extent of retrograde amnesia (in years). Separate correlations were computed for the MCI group and the H and MTL group. Because there is an advantage in using the same kind of test to assess both kinds of impairment (Kopelman, 2000; Mayes, Daum, Markowisch, & Sauter, 1997), we also assessed the relationship between anterograde and retrograde amnesia when both scores were taken from

the news events test for the nine individuals with MCI and for the 10 H and MTL patients for whom both scores were available.

Measuring the amount of disproportionate retrograde amnesia. To identify the amount of retrograde amnesia that was disproportionate to the severity of anterograde amnesia, the temporal extent of retrograde amnesia predicted by the regression line computed from the correlation analysis for the H and MTL patients was subtracted from the temporal extent of retrograde amnesia exhibited by each individual with MCI. Thus, when the anterograde amnesia score for an individual with MCI was less than a *z* score of −3.4, the regression line predicted no retrograde amnesia. Accordingly, in these cases, the amount of disproportionate retrograde amnesia was equivalent to the extent of retrograde amnesia exhibited by that individual. Ten of the 15 individuals with MCI fit this circumstance. For each of the other five individuals with MCI, the amount of disproportionate retrograde amnesia was equivalent to the difference between the temporal extent of retrograde amnesia exhibited by the individual and the temporal extent of retrograde amnesia predicted (from the regression line) by an H or MTL patient with the same amount of anterograde amnesia. To identify whether the MCI group exhibited retrograde amnesia that was disproportionate to the severity of their anterograde amnesia, the mean score was compared with zero using a single-sample *t* test.

Analysis plan. The severity of anterograde and retrograde amnesia was compared between the MCI group and the H and MTL group using a repeated measures two-way ANOVA (Type of Amnesia × Group). Follow-up between-subjects *t* tests comparing the two groups were carried out for the severity of anterograde and retrograde amnesia. The relationship between the severity of anterograde and retrograde amnesia was calculated separately for the H and MTL group and the MCI group using Pearson's *r*. Arithmetic means and standard errors of the means are reported.

Results

Relating anterograde and retrograde memory in MCI and MTL amnesia. Figure 2 shows the severity of anterograde amnesia (based on the four conventional anterograde memory tests) and the temporal extent of retrograde amnesia for the MCI group[1] (and H and MTL group for comparison). The severities of anterograde and retrograde amnesia were different for the MCI group and for the H and MTL group (interaction, $F[1, 24] = 8.3$, $p < .01$). Specifically, the MCI group exhibited less severe anterograde amnesia, $t(24) = 4.2$, $p < .001$, but more severe retrograde amnesia, $t(24) = 3.3$, $p < .005$, than the H and MTL group.

Figure 3 shows the relationship between the severity of anterograde amnesia and the temporal extent of retrograde amnesia for individuals with MCI and for individual H and MTL patients. Although the severity of anterograde and retrograde amnesia was closely related in H and MTL patients ($r = .77$, $p < .01$), these measures were only weakly related in the MCI group ($r = .34$, $p > .20$). Moreover, the scores for all the individuals with MCI (except the individual who exhibited no detectable retrograde amnesia) lay outside the 95% confidence intervals for the regression line created from the scores of the H and MTL patients. This result indicates that, based on the relationship between anterograde and retrograde amnesia observed for H and MTL patients, the retrograde amnesia exhibited by the MCI group was disproportionate to anterograde amnesia. Specifically, the MCI group exhibited 30.4 ± 5.4 more years of retrograde amnesia on average than would be expected from the severity of their anterograde amnesia, $t(10) = 5.2$, $p < .001$.

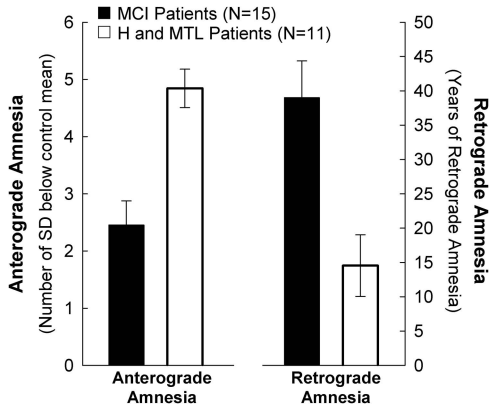

Figure 2. Experiment 2: Severity of anterograde amnesia and semantic retrograde amnesia for the mild cognitive impairment (MCI) group and for a group of patients with bilateral lesions of hippocampus (H) or larger medial temporal lobe (MTL) lesions (H and MTL data from Smith et al., 2013). H and MTL patients exhibited severe anterograde amnesia and limited retrograde amnesia. In contrast, the MCI group exhibited limited anterograde amnesia and severe retrograde amnesia. The dissociation between group and type of amnesia was significant ($p < .01$). The anterograde amnesia score was derived from four tests of new learning ability (see Experiment 1, Method and Table 1). The retrograde amnesia score represents the severity of retrograde amnesia (duration in years), calculated from the number of 5-year time periods in which recall performance of an individual with memory impairment was significantly below control performance (see Experiment 1, Method). For both anterograde scores and retrograde scores, higher scores indicate more severe impairment. Error bars indicate standard error of the mean.

Relating anterograde and retrograde memory with the same test. We also assessed the relationship between anterograde and retrograde amnesia for the MCI group and the H and MTL group when both scores were taken from the news events test. The finding of disproportionate retrograde amnesia in the MCI group was similar when anterograde memory was based on the news events test and when it was based on the four conventional measures of anterograde memory. That is, the MCI group still exhibited disproportionate retrograde amnesia relative to anterograde amnesia when both anterograde and retrograde amnesia were calculated from the news events test. Specifically, they exhibited 21.6 ± 3.1 more years of retrograde amnesia on average than would be expected from the severity of their anterograde amnesia, $t(8) = 5.7$, $p < .001$.

Experiment 3: Relating Predictions From Behavioral Findings to Brain Measures in the MCI Group

Three predictions about the brain emerged from the findings of Experiments 1 and 2 regarding the severity of anterograde and retrograde amnesia in MCI. First, the finding that the MCI group

[1] Note that when the estimate for the temporal extent of retrograde amnesia for the MCI group was based on all 21 controls (39.0 ± 5.3 years; see Figure 2), it was almost identical to when it was based on only the 15 controls who completed both the four anterograde tests and as well as the retrograde test (38.7 ± 5.1 years).

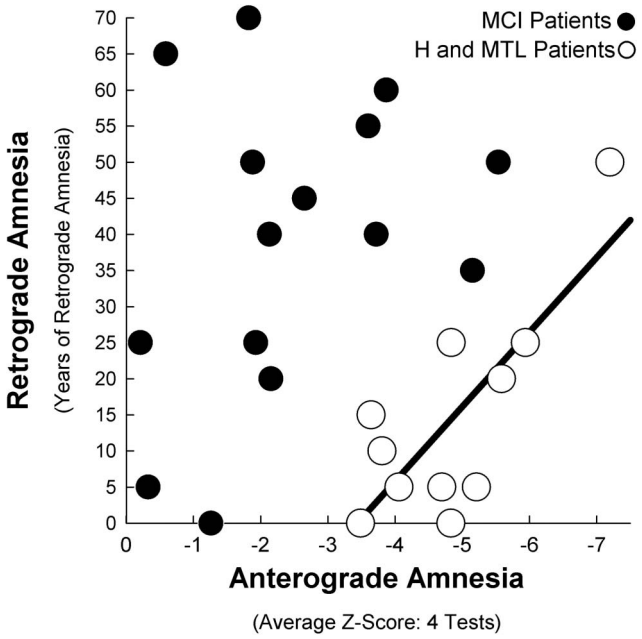

Figure 3. Experiment 2: Individual scores showing the relationship between the severity of anterograde amnesia and the severity of retrograde amnesia for the 15 individuals with mild cognitive impairment (MCI; black circles) and the 11 patients with bilateral lesions to hippocampus (H) or larger medial temporal lobe (MTL) lesions (white circles). The black regression line was based on the data from the H and MTL patients (Smith et al., 2013). There was a close relationship between anterograde amnesia and retrograde amnesia for the H and MTL patients ($r = .77$, $p < .01$). For the MCI group, the relationship was weak ($r = .34$, $p > .20$) and retrograde amnesia was variable. All individuals with MCI (except the single individual with no detectable retrograde amnesia) lay outside the 95% confidence intervals for the regression line. The anterograde amnesia score was derived from four tests of new learning ability (see Experiment 1, Method and Table 1). The retrograde amnesia score represents the severity of retrograde amnesia (duration in years), calculated from the number of 5-year time periods in which recall performance of an individual with memory impairment was significantly below control performance. For anterograde amnesia lower scores indicate more severe impairment, whereas for retrograde amnesia higher scores indicate more severe impairment.

had less severe anterograde amnesia than H and MTL patients (see Figure 2) suggests that they also have less severe atrophy of the MTL. Second, because anterograde and retrograde amnesia have an orderly relationship when atrophy is limited to the MTL (see Figure 3, H and MTL patients), one might suppose that individuals who deviate from that relationship have atrophy outside the MTL. Accordingly, the second prediction is that the MCI group has significant atrophy that extends beyond the MTL. The third prediction follows from the second. The extent to which the severity of retrograde amnesia in MCI is disproportionate to the severity of anterograde amnesia will be related to the integrity of cortical regions outside the MTL. These three predictions were tested for 11 of the 15 individuals in the MCI group for whom structural brain scans were available. Because structural scans were available for only these 11 individuals, analyses were limited to testing the three predictions that emerged from the behavioral findings and to the brain regions of interest (see A priori areas of interest).

Brain measures were evaluated to test three predictions that emerged from the behavioral findings. Regional brain volumes and neocortical thickness were first measured for the MCI group and then compared with controls. Correlations were then carried out between brain measures in the MCI group and the severity of anterograde amnesia (composite *z* score from four conventional tests) and the temporal extent of disproportionate retrograde amnesia (in years).

Method

Participants. Eleven individuals from the MCI group in Experiments 1 and 2 participated (two females, 78.5 ± 2.0 years of age). The other four individuals with MCI were either unavailable or ineligible for magnetic resonance imaging (MRI). For comparison, structural MRI scans were obtained for 11 healthy control participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.ucla.edu). In addition, percent reductions in the volumes of the hippocampus and parahippocampal gyrus are reported for nine of the 11 H and MTL patients reported in Experiment 2 for comparison. For two H patients (patients RB and GD), MRI scans were not available.

Obligatory statement regarding the ADNI objective. The ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations as a $60-million, 5-year public–private partnership. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials. The principal investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California – San Francisco. ADNI is the result of efforts of many coinvestigators from a broad range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the United States and Canada. The initial goal of ADNI was to recruit 800 subjects, but ADNI has been followed by ADNI-GO and ADNI-2. To date, these three protocols have recruited over 1,500 adults, ages 55 to 90, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow-up duration of each group is specified in the protocols for ADNI-1, ADNI-2 and ADNI-GO. Subjects originally recruited for ADNI-1 and ADNI-GO had the option to be followed in ADNI-2 (for up-to-date information, see http://www.adni-info.org).

Measuring regional brain volumes and neocortical thickness.

Image acquisition and processing. High-resolution, T1-weighted, structural MRI scans were obtained for participants in the MCI group. The scans were acquired on a General Electric (GE) 1.5T scanner at the UCSD Radiology Imaging Laboratory (four individuals) or on a GE 3T scanner at the UCSD Center for Functional MRI (seven individuals). For all individuals with MCI, an 8-channel, high-resolution head coil was used. In-plane resolu-

tion was 1 × 1 mm and thickness was 1 or 1.2 mm (echo times: 2.8 to 3.9 s; repetition times: 6.5 to 8.8 s; flip angles: 8 or 12 degrees). The average interval between the completion of behavioral testing and acquisition of the brain scan was 3.5 ± 1.4 months for the MCI group. For the control group, raw dicom files from high-resolution, T1-weighted, structural MCI scans were obtained from ADNI in August 2010. The controls were matched to the 11 individuals with MCI on the basis of age (79.1 ± 1.6 years of age), sex (two female), magnet strength (four controls scanned at 1.5T and seven controls scanned at 3T), as well as manufacturer and type of head coil (i.e., GE scanner with an 8-channel head coil). For two individuals with MCI, control scans were selected that matched the individual based on age, sex, and magnet strength, but that had been acquired on a Siemens scanner.

Measures of cortical thickness, cortical volume, and hippocampal volume were calculated for the MCI and control groups using FreeSurfer software (version 5.1; Dale, Fischl, & Sereno, 1999; Fischl et al., 2002, 2004; Fischl, Sereno, & Dale, 1999). Briefly, the automated software divides the brain into cortical gray matter, white matter, cerebrospinal fluid (CSF), and deep, gray-matter structures. Next, each voxel within the cerebral cortex is assigned a neuroanatomical label according to a probabilistic atlas (Desikan et al., 2006). For volume segmentation and cortical surface reconstruction, the cortical surface is divided into 34 distinct areas in each hemisphere. Cortical thickness of each area is calculated as the distance from the gray–white boundary to the gray–CSF boundary, averaging across multiple measurements within each area. Cortical thickness does not depend on head size, so this measure was not adjusted for intracranial volume. However, cortical volumes and hippocampal volume were adjusted relative to intracranial volume as calculated by FreeSurfer (estimated total intracranial volume; Buckner et al., 2004). Manual intervention was carried out to correct errors associated with distinctions between brain and pia-skull boundaries, and between gray matter and white matter boundaries. Implementation of these corrections was carried out blind to group membership.

For the nine H and MTL patients for whom structural MRI scans were available, volumes for the hippocampus and parahippocampal gyrus were estimated based on high-resolution, T1-weighted magnetic resonance images. The scores were compared with 19 age-matched, healthy males for patients KE, EP, GP, RS, GW, and JRW, and 11 age-matched, healthy females for patient LJ (Gold & Squire, 2005). These brain measures have been reported previously (Bayley et al., 2006; Press, Amaral, & Squire, 1989; Smith et al., 2013). Briefly, the hippocampus and parahippocampal gyrus (temporopolar cortex, entorhinal cortex, perirhinal cortex, and parahippocampal cortex) were drawn on the structural MRI images according to histological landmarks readily visible on MRI (Frankó, Insausti, Artacho-Perula, Insausti, & Chavoix, 2014; Insausti et al., 1998). Values for the left and right hemispheres were combined. The volume of each region was then divided by the total brain volume. For patients LM and WH, the percent reduction scores were based on measurements of the average area of the hippocampus and parahippocampal gyrus obtained from three consecutive 5-mm images from T1-weighted, structural MRI scans (starting from the pes hippocampus and proceeding caudally). The areas for the left and right hemispheres were then combined. The area of each region was then divided by the total area of the temporal lobe bilaterally (from the fundi of the collateral sulcus to the inferior limiting sulci of the insular cortex). The scores for these two patients were compared with four controls, as previously reported by Press et al. (1989).

The percent volume reduction measure was calculated for all individuals in the MCI and the H and MTL groups relative to their respective controls. To determine if each group exhibited smaller volumes of the hippocampus and parahippocampal gyrus, the percent volume reductions were compared with zero using a one-sample *t* test.

A priori areas of interest. Analyses were carried out for seven brain areas of interest. These were areas previously related to the severity of retrograde amnesia (Barr, Goldberg, Wasserstein, & Novelly, 1990; Bayley et al., 2005, 2006; Bright et al., 2006; Eustache et al., 2004; Kopelman, 1991; Kopelman et al., 2003; O'Connor, Butters, Miliotis, Eslinger, & Cermak, 1992; Reed & Squire, 1998), areas in which atrophy has previously been reported in MCI (Bakkour et al., 2009; Fennema-Notestine et al., 2009; McDonald et al., 2009; McEvoy et al., 2009; Whitwell et al., 2007), or areas in which atrophy has been associated with decline from MCI to probable AD (Bakkour et al., 2009; McEvoy et al., 2009; Whitwell et al., 2007). The seven areas were as follows: hippocampus, parahippocampal gyrus, lateral temporal cortex, inferior parietal lobule, precuneus, posterior cingulate gyrus, and the prefrontal cortex.

Analysis plan. The objective was to identify brain areas in which measures (volumes and cortical thickness) were different between the MCI group and controls, or to identify if brain measures were associated with behavioral measures (anterograde or retrograde amnesia). Statistical tests were carried out for each of the seven a priori areas of interest. When necessary, the areas computed by FreeSurfer were combined together to obtain the measures for an area of interest (parahippocampal gyrus = temporal pole + entorhinal cortex + parahippocampal cortex; lateral temporal cortex = fusiform gyrus + inferior + middle + superior temporal gyri; posterior cingulate gyrus = posterior cingulate cortex + isthmus cingulate; prefrontal cortex = caudal and rostral anterior cingulate gyri + caudal and rostral middle frontal gyri + lateral and medial orbitofrontal gyri + paracentral lobule + pars opercularis + pars orbitalis + pars triangularis + superior frontal gyrus + frontal pole). For volume measures, the values were summed together prior to correcting for intracranial volume. For thickness measures, the values were combined using a weighted average based on surface area. These methods were carried out separately for each hemisphere. Measures of regional brain volumes and neocortical thickness for the MCI group and controls were compared using between-subjects *t* tests. Detection of between-groups differences may be affected by differences in scanner strength (Han et al., 2006). Accordingly, tests comparing brain measures between the MCI group and controls included a covariate for scanner strength (1.5T or 3T). By contrast, detection of within-subject brain–behavior relationships is robust to differences in field strength (Dickerson et al., 2008). Accordingly, correlational analyses investigating the relationship between brain measures and behavioral measures within the MCI group did not include scanner strength as a covariate. Within the MCI group, the relationships between brain measures (brain volumes, neocortical thicknesses) and behavioral measures (anterograde amnesia, retrograde amnesia) were assessed with Pearson's *r*. Because age and education were uncorrelated with the severity of anterograde and retrograde amnesia (see Experiment 1, Method), these measures were not included as covariates in the brain–behavior correlations. Probabilities (uncorrected for multiple comparisons) are reported for each a priori area of interest. If a statistical test was significant for the left or right hemispheres for each

region of interest, a bilateral test was also carried out. For completeness, significant results obtained in areas other than the a priori areas of interest are reported as well. Arithmetic means and standard errors of the means are reported.

Finally, a best subsets regression analysis was carried out to determine which variables best predicted the amount of disproportionate retrograde amnesia in the MCI group. For this analysis, the predictor variables were the five brain regions associated with the amount of disproportionate retrograde amnesia (see Table 2 and Results, Prediction 3, which follows) and ApoE status (see Table 1). Follow-up linear regression analyses were carried out on the regression models with the fewest predictors and that explained the most variance (according to adjusted R^2).

Results

Prediction 1: The MCI group will exhibit less severe MTL atrophy than the H and MTL group. As indicated by structural MRI scans, compared to controls, the MCI group had a smaller volume of the hippocampus bilaterally (18.7 ± 3.9% reduction in volume) and parahippocampal gyrus bilaterally (16.5 ± 4.3% reduction in volume) (see Table 2). In addition, parahippocampal gyrus bilaterally was 10.4 ± 3.2% thinner in the MCI group relative to controls (Table 2 and Figure 4). The H and MTL group exhibited significant volume reduction in the hippocampus (55.9 ± 8.5% reduction, $t[8] = 6.4$, $p < .001$). For the parahippocampal gyrus, the two MTL patients exhibited substantial volume reduction in the parahippocampal gyrus (94.0 ± 0.0% reduction in volume), whereas the seven H patients exhibited almost none (1.7 ± 4.1% reduction in volume). As a group, the H and MTL patients did not exhibit significant volume reduction in the parahippocampal gyrus (22.2 ± 13.9% reduction, $t[8] = 1.6$, $p > .10$). Accordingly, volume reduction in the hippocampus was less severe in the MCI group than in the H and MTL group, $t(11.3) = 3.9$, $p < .005$, whereas volume reduction in the parahippocampal gyrus was similar for the two groups, $t(9.5) = 0.4$, $p > .70$. Thus, consistent with Prediction 1, volume loss in the MTL was less severe in the MCI group than in the H and MTL group.

Interestingly, the severity of anterograde amnesia in the MCI group, as measured by the four conventional anterograde memory

Table 2
Experiment 3: Brain Measures for the MCI and Control Groups

	Control group (n = 11)		MCI group (n = 11)							
					Effect size (MCI v Control)		Correlation with retrograde amnesia		Correlation with anterograde amnesia	
	Mean (*SEM*)		Mean (*SEM*)		Cohen's *d*		Pearson *r*		Pearson *r*	
Region of interest	VOL	THK	VOL	THK	VOL	THK	VOL	THK	VOL	THK
Medial temporal lobe										
L hippocampus	.229 (.010)	—	.182 (.009)	—	**1.5****	—	**.59**†	—	**.76***	—
R hippocampus	.239 (.011)	—	.199 (.011)	—	**1.1****	—	.50	—	**.56**†	—
Bil. hippocampus	.468 (.021)	—	.381 (.018)	—	**1.3****	—	**.61***	—	**.74****	—
L parahippocampal gyrus	.377 (.013)	2.95 (.08)	.327 (.019)	2.68 (.10)	**0.9***	**0.9**†	**.33**[a]	−.03	**.48**[a]	.16
R parahippocampal gyrus	.364 (.012)	3.01 (.09)	.292 (.016)	2.65 (.12)	**1.5****	**1.1***	.43	.23	.17	−.14
Bil. parahippocampal gyrus	.742 (.023)	2.98 (.07)	.620 (.032)	2.67 (.10)	**1.3****	**1.1***	.41	.12	.38	.00
Neocortex										
L lateral temporal cortex	2.525 (.077)	2.46 (.03)	2.436 (.087)	2.35 (.06)	0.3	0.7	.47	−.17	.08	.13
R lateral temporal cortex	2.510 (.060)	2.52 (.02)	2.456 (.086)	2.39 (.06)	0.2	**0.9***	**.56**†[b]	−.03	.08	−.07
Bil. lateral temporal cortex	5.035 (.136)	2.49 (.02)	4.892 (.167)	2.37 (.05)	0.3	**0.9**†	**.53**†	−.07	.06	.03
L inferior parietal lobule	.712 (.027)	2.25 (.05)	.758 (.049)	2.29 (.05)	−0.4	−0.2	.23	−.02	.35	−.03
R inferior parietal lobule	.889 (.036)	2.24 (.04)	.889 (.052)	2.28 (.06)	−0.0	−0.2	.46	−.17	.36	.15
L precuneus	.535 (.022)	2.17 (.05)	.521 (.005)	2.16 (.05)	0.2	0.0	.24	−.12	.17	.01
R precuneus	.521 (.018)	2.11 (.04)	.537 (.023)	2.11 (.06)	−0.2	0.0	.04	−.05	−.17	.06
L posterior cingulate gyrus	.328 (.011)	2.32 (.04)	.327 (.012)	2.31 (.07)	0.0	0.1	**.46**[c]	.35	−.05	.36
R posterior cingulate gyrus	.317 (.013)	2.35 (.05)	.325 (.014)	2.26 (.04)	−0.2	0.6	−.10	−.22	−.38	.00
L prefrontal cortex	4.151 (.109)	2.36 (.03)	4.373 (.143)	2.33 (.06)	**−0.5***	0.2	.19	−.30	.16	−.32
R prefrontal cortex	4.117 (.096)	2.35 (.03)	4.332 (.114)	2.31 (.05)	**−0.6***	0.3	.17	−.27	.22	−.37
Bil. prefrontal cortex	8.268 (.203)	2.35 (.03)	8.704 (.276)	2.32 (.05)	−0.5	**0.2**[d]	.19	−.29	.19	−.35

Note. Means (and standard error of the mean; *SEM*) for volume (VOL) and thickness (THK, mm) for the mild cognitive impairment (MCI) group and the control group for seven regions of interest (see Experiment 3, Method). Volume measures for each region denote the percentage of total intracranial volume. Brain–behavior correlations were carried out to relate volume and thickness measures to anterograde amnesia (derived from four tests of new learning ability) and retrograde amnesia (derived from a test of notable news events) in the MCI group. The measure of retrograde amnesia was the extent to which the severity of retrograde amnesia was disproportionate to the severity of anterograde amnesia (see Experiment 2, Method). Effect sizes for differences between the MCI and control groups are reported as Cohen's *d* and reflect the difference between the means, in standard deviations. Effect sizes for the brain–behavior correlations are reported as Pearson *r*. Significant effects are highlighted in bold text. L = left; R = right; Bil. = bilateral.
[a] Parahippocampal cortex was marginally significant when examined separately ($p < .07$). [b] The correlation was stronger ($r = .59$, $p < .06$) when the fusiform gyrus was omitted. [c] Posterior cingulate cortex was significant when examined separately ($r = .64$, $p < .05$). [d] Ventrolateral prefrontal cortex was significant when examined separately ($p < .01$).
† $p < .10$. * $p < .05$. ** $p < .01$.

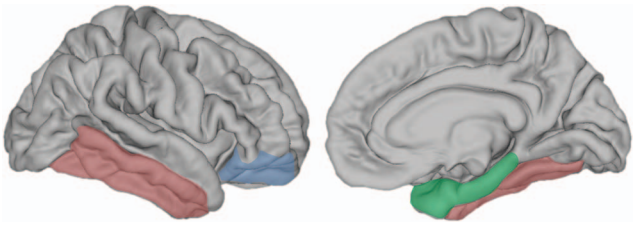

Figure 4. Brain regions in which neocortex was thinner in the mild cognitive impairment (MCI) group ($n = 11$) compared with controls ($n = 11$; lateral view on the left, medial view on the right). The MCI group exhibited thinner cortex (and smaller volumes) in the structures of the medial temporal lobe (MTL; parahippocampal gyrus 10% thinner and 16% reduced in volume [green] and hippocampus [H] 19% reduced in volume [not pictured]). Consistent with Prediction 1 (see Experiment 3), the reduction in volume of MTL structures was less severe in the MCI group than in the H and MTL group. Consistent with Prediction 2 (see Experiment 3), the MCI group also exhibited atrophy of areas outside of the MTL. Specifically, neocortex was 6% and 7% thinner than controls bilaterally in lateral temporal cortex (red) and bilaterally in ventrolateral prefrontal cortex (blue), respectively. The lateral temporal cortex includes fusiform, inferior temporal, and middle temporal gyri. Ventrolateral prefrontal cortex includes lateral orbitofrontal and parsorbitalis cortices. Parahippocampal gyrus includes temporopolar, entorhinal, and parahippocampal cortices. All comparisons between the MCI group and controls were significant at $p < .05$.

tests, was related to the volume of the hippocampus bilaterally ($r = .74$, $p < .01$; Table 2). Anterograde amnesia was also weakly related to the volume of the left parahippocampal cortex ($r = .57$, $p < .07$) and significantly related to the volume of the left caudal anterior cingulate ($r = .64$, $p < .05$). For all these areas, more severe anterograde amnesia was associated with smaller volumes. Measures of cortical thickness were not correlated with the severity of anterograde amnesia.

Prediction 2: The MCI group will exhibit significant brain atrophy that extends beyond the MTL. Consistent with Prediction 2, the MCI group exhibited significantly thinner neocortex outside of the MTL (Table 2 and Figure 4). Specifically, cortex was thinner in the MCI group than in controls in the right lateral temporal cortex (5.2 ± 2.2% thinner), and was thinner bilaterally when the superior temporal gyrus was excluded (6.1 ± 2.1% thinner, $t[20] = 2.7$, $p < .05$). In addition, thinner cortex was observed in the MCI group relative to controls in two adjacent areas in the ventrolateral prefrontal cortex (bilateral pars orbitalis, 8.2 ± 2.7% thinner, $t[20] = 3.5$, $p < .01$; bilateral lateral orbitofrontal gyrus, 6.1 ± 2.9% thinner, $t[20] = 3.1$, $p < .01$). Measures of neocortical volume outside the MTL did not differ between the MCI group and controls (see Table 2), except for the left and right prefrontal cortex, which were a little larger in the MCI group than in controls (5.3 ± 3.4% and 5.2 ± 3.3% larger, respectively; note, however, that the volume of prefrontal cortex bilaterally was not different between the MCI and control groups, $t[20] = 1.6$, $p > .10$).

Prediction 3: The degree that retrograde amnesia is disproportionate to anterograde amnesia will be related to the integrity of neocortical brain regions. Consistent with Prediction 3, the amount of disproportionate retrograde amnesia in MCI was related to the volume of the left posterior cingulate cortex ($r = .64$, $p < .05$) and the paracentral lobule bilaterally ($r = .60$, $p < .05$), a region adjacent to the posterior cingulate cortex. The amount of disproportionate retrograde amnesia was also (marginally) related to the volume of bilateral lateral temporal cortex ($r = .53$, $p < .10$; Table 2). A stronger relationship was observed for the right lateral temporal cortex when the fusiform gyrus was excluded ($r = .59$, $p < .06$). For all these regions, smaller volumes were associated with more disproportionate retrograde amnesia (see Figure 5). A relationship was also observed between the amount of disproportionate retrograde amnesia and the volume of the hippocampus bilaterally ($r = .61$, $p < .05$; Table 2), and a marginal relationship was observed for the volume of the left parahippocampal cortex ($r = .58$, $p < .07$), though the volumes of these regions were also related to the severity of anterograde amnesia. It is important to note that the amount of disproportionate retrograde amnesia was not related to the volumes in the areas of prefrontal cortex that were thinner in the MCI group relative to controls (bilateral pars orbitalis, $r = -0.42$, $p > .20$; bilateral lateral orbitofrontal gyrus, $r = .16$, $p > .60$), nor was it related to the volume of the prefrontal cortex as a whole (see Table 2). Measures of neocortical thickness outside of the MTL were not correlated with the disproportionality of retrograde amnesia in the MCI group (see Table 2). Thus, regions in the MTL were related to the severity of both anterograde and retrograde amnesia, whereas neocortical regions outside the MTL were related only to the severity of retrograde amnesia.

Next, we asked which variables best predicted the amount of disproportionate retrograde amnesia in the MCI group. A best subsets regression analysis was carried out using the five brain regions that were significantly or marginally correlated with the amount of disproportionate retrograde amnesia (see Table 2; hippocampus bilaterally, left parahippocampal cortex, right lateral temporal cortex [minus the fusiform gyrus], left posterior cingulate cortex, and paracentral lobule bilaterally). In addition, ApoE status was included as a predictor because it was closely related to the severity of retrograde amnesia (see Table 1 and Experiment 1). The best subsets regression analysis indicated that adjusted *R*-squared was highest for a model that included ApoE status and the hippocampus and paracentral lobule bilaterally. A follow-up linear regression analysis revealed that these three variables could

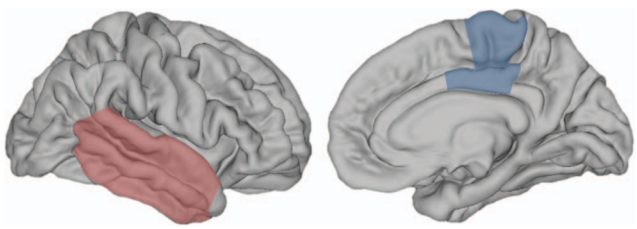

Figure 5. Consistent with Prediction 3 (see Experiment 3), smaller volumes of the right lateral temporal cortex ($p < .06$; red) and the left posterior cingulate cortex, and the paracentral lobule bilaterally (p values <0.05; blue), were associated with the extent to which the severity of retrograde amnesia was disproportionate to the severity of anterograde amnesia in the mild cognitive impairment (MCI) group ($n = 11$; see Experiment 2, Measuring the amount of disproportionate retrograde amnesia). The lateral temporal cortex includes inferior, middle, and superior temporal gyri. The lateral view of the brain is on the left and the medial view of the brain is on the right.

reliably predict the amount of disproportionate retrograde amnesia in the MCI group (adjusted $R^2 = 0.56$; $F[3, 7] = 5.3$, $p < .05$).

Discussion

Anterograde memory and retrograde memory for news events were assessed in 15 individuals with MCI and in controls. For the MCI group, anterograde memory was modestly impaired (see Table 1). In contrast to the modest anterograde memory impairment exhibited by the MCI group, retrograde amnesia for news events was severe and spanned nearly 40 years before the onset of amnesia (Figure 1 and Table 1). The severity of retrograde amnesia (and not the severity of anterograde amnesia or other measures of cognitive status), was most predictive of heritable risk of AD and conversion to probable AD in the MCI group (see Table 1).

Interestingly, compared with a group of 11 patients with acute damage limited to hippocampus or larger lesions of the MTL, the MCI group exhibited less severe anterograde amnesia and more temporally extensive retrograde amnesia (see Figure 2). The severity of retrograde amnesia exhibited by the MCI group was disproportionate to their anterograde amnesia (whether anterograde amnesia was assessed by the test of news events or was assessed by the four conventional anterograde memory tests) and was more severe than would have been expected if their atrophy was limited to the MTL (see Figure 3).

These behavioral findings generated three predictions regarding the integrity of brain regions in the MCI group. First, relative to H and MTL patients, the more modest anterograde amnesia exhibited by the MCI group should also be associated with more modest MTL atrophy. This prediction was confirmed for the hippocampus bilaterally (see Table 2). Second, individuals with MCI who deviate from the orderly relationship between anterograde and retrograde amnesia exhibited by H and MTL patients would be expected to have atrophy outside the MTL. This expectation was confirmed by an analysis of cortical thickness in the MCI group, which revealed that lateral temporal cortex bilaterally and ventrolateral prefrontal cortex bilaterally were thinner than in controls (Table 2, Figure 4). Third, the extent to which the severity of retrograde amnesia was disproportionate to the severity of anterograde amnesia should be related to the integrity of neocortical regions outside the MTL. The volumes of three areas in neocortex (Table 2 and Figure 5) were related to the disproportionality of retrograde amnesia in the MCI group (right lateral temporal cortex, left posterior cingulate cortex, and paracentral lobule bilaterally). Overall, the pattern was that the integrity of the MTL was associated with both anterograde and retrograde amnesia, whereas the integrity of neocortical regions were uniquely associated with the disproportionality of retrograde amnesia relative to anterograde amnesia (note that because of the relatively small sample size [$n = 11$] for the brain analyses, it is possible that the present findings do not identify all the relevant brain regions important for anterograde or retrograde amnesia). Finally, the volumes of both the paracentral lobule and hippocampus bilaterally (in conjunction with ApoE status) were successful at predicting the amount of disproportionate retrograde amnesia in the MCI group.

When identifying the year of onset of amnesia in individuals with MCI, some time must undoubtedly elapse between the onset of symptoms and the time when the diagnosis can be made. The decline from healthy cognitive status to a level of function consistent with a diagnosis of MCI typically occurs within about 5 years (Acosta-Baena et al., 2011; Marquis et al., 2002). Accordingly, performance on some parts of the news events test could reflect impaired anterograde memory, that is, impaired memory for events that occurred after the onset of symptoms but before diagnosis. Thus, the estimate for the temporal extent of retrograde amnesia in MCI could be as much as 5 years too long. Yet, even allowing for a 5-year error in the estimate, the MCI group still exhibited severe retrograde amnesia that was disproportionate to the severity of their anterograde amnesia (i.e., see Figure 3, and subtract 5 years from the retrograde amnesia score of each member of the MCI group).

We considered using a test of autobiographical memory, in addition to the news events test. Unfortunately, the tools available to measure autobiographical memory do not easily lend themselves to the analysis carried out here. Specifically, most of the tests (Kopelman, Wilson, & Baddeley, 1989; Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002) sample only a few time periods. Better tests could be constructed (see Bayley, Hopkins, & Squire, 2003, for use of the method introduced by Crovitz & Schiffman, 1974), but even then it would be difficult to achieve the 5-year temporal resolution across the life span that is available from the news events test. In any case, the present findings relate to the relationship between anterograde amnesia and retrograde amnesia for news events. A different relationship might be observed between anterograde amnesia and retrograde amnesia for autobiographical information.

The volume loss in lateral temporal cortex of the MCI group may be particularly important for understanding their retrograde amnesia. In other individuals with damage to lateral temporal cortex (as the result of temporal lobectomy, encephalitis, or an abscess), damage to this region has been associated with severe retrograde amnesia that appeared disproportionate to the severity of anterograde amnesia (Barr et al., 1990; Bright et al., 2006; O'Connor, et al., 1992; Reed & Squire, 1998). Additionally, the integrity of lateral temporal cortex in AD and MCI has been previously associated with memory for semantic retrograde memory (Barbeau et al., 2012; Gilboa et al., 2005; Woodard et al., 2009). It is possible that variability in the integrity of lateral temporal cortex, in addition to the hippocampus, paracentral lobule, and ApoE status (as revealed by the best subsets regression analysis in Experiment 3) might account for differences in the severity of retrograde amnesia that have been reported in studies of MCI (Leyhe et al., 2009, 2010; Murphy et al., 2008; Seidenberg et al., 2009; Thomann et al., 2012).

Frontal lobe damage and lateral temporal lobe damage have both been associated with retrograde amnesia (Bayley et al., 2005; Kopelman, 1991; Kopelman et al., 1999, 2003; Kroll et al., 1997). In the present study, we found no relationship in the MCI group between retrograde amnesia and the integrity of the prefrontal cortex. Though the MCI group exhibited thinner cortex in ventrolateral prefrontal cortex bilaterally, neither the thickness nor volume of this area was related to their disproportionate retrograde amnesia (in addition, the volumes of the left and right prefrontal cortex were larger in the MCI group than in controls; see Table 2). Thus, their disproportionate retrograde amnesia is likely related to the integrity of lateral temporal neocortex rather than to the integrity of frontal neocortex.

If the severity of retrograde amnesia in MCI is related to atrophic changes in neocortex, which stores (at least in part) the content of semantic memory, why then does the MCI group exhibit retrograde amnesia that is temporally limited? Should not all memories be compromised regardless whether they are recent or remote? One way to understand the sparing of remote memory in MCI is to suppose that memories become strengthened with repeated rehearsal, and that the oldest memories have the most opportunity for rehearsal or replay and subsequent strengthening (Fuster, 2009; McClelland, McNaughton, & O'Reilly, 1995; Moscovitch, Nadel, Winocur, Gilboa, & Rosenbaum, 2006). Indeed, in healthy adults and in AD, how often memories have been retrieved was a better predictor of news event memory than how long ago the event had occurred (Müller et al., 2014). Likewise, memories that are especially personally significant (and that are also likely to be strong) tend to be less vulnerable to disruption in AD (Martinelli, Anssens, Sperduti, & Piolino, 2013). According to this idea, when neocortex is compromised, the stronger memories are more likely to be spared than weaker memories, and memories are strongest in the most remote time periods.

Measures of semantic retrograde memory, such as the news events test, may be particularly sensitive predictors of cognitive decline and conversion to AD. In the present study, the members of the MCI group who converted to probable AD in the 3 years following testing had approximately 20 more years of retrograde amnesia than the members who remained stable during that time frame. Consistent with this finding, performance of healthy adults on a test of famous names from the remote past (individuals who became famous 45 to 60 years prior to testing) predicted cognitive decline across 1.5 years (Seidenberg et al., 2013). Furthermore, brain activity in a network of brain regions (including lateral temporal cortex and posterior cingulate gyrus) by the same individuals when performing this task also predicted cognitive decline across the same time period (Woodard et al., 2010). It is notable that another study of MCI, which used a combined measure of semantic memory (famous faces, general facts, and public events), did not predict conversion to AD during a 3-year period (Barbeau et al., 2012). It would be interesting to analyze the data in that study separately for public events. Performance on semantic memory tests for public events or famous people may be more predictive of cognitive decline and conversion to AD than performance on tests concerning general knowledge.

In summary, the MCI group exhibited only modest anterograde amnesia, but extensive retrograde amnesia for news events, compared with patients with lesions limited the H and MTL. Compared with a group of H and MTL patients, given the modest severity of anterograde amnesia in the MCI group, the severity of their retrograde amnesia was greater than would have been expected if their atrophy were limited to the MTL. The modest severity of the anterograde amnesia corresponded to modest atrophy in the MTL, whereas the severe retrograde amnesia corresponded to atrophy in three neocortical regions. Volumes of structures in the MTL were related to both anterograde and retrograde amnesia, whereas volumes in specific regions of neocortex were related only to the degree that the temporal extent of retrograde amnesia was disproportionate to the severity of anterograde amnesia. The amount of disproportionate retrograde amnesia in the MCI group was best predicted by a model that incorporated heritable risk for AD in addition to the integrity of MTL and neocortical structures.

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Supplemental Table 1.
Experiment 2. Characteristics of memory-impaired H and MTL patients

Patient	Sex	Age (yrs)	Education (yrs)	Anatomical Findings	IQ (WAIS-R)	WMS-R				
						Attention	Verbal	Visual	General	Delay
RB	M	53	10	H*	103	---	---	---	---	---
GD	M	45	12	H*	92	109	86	88	85	60
WH	M	64	17	H	113	88	72	82	67	<50
LM	M	55	15	H	109	124	94	82	89	62
EP	M	79	12	MTL	98	94	59	92	68	56
KE	M	64	13.5	H	108	114	64	84	72	55
LJ	F	68	12	H	101	104	85	87	81	54
GP	M	57	16	MTL	98	102	79	62	66	<50
RS	M	49	12	H	99	99	85	81	82	<50
GW	M	46	12	H	108	105	67	86	70	<50
JRW	M	42	12	H	90	87	65	95	70	<50

Note. The Wechsler Adult Intelligence Scale-Revised (WAIS-R) and the Wechsler Memory-Scale Revised (WMS-R) yield mean scores of 100 in the normal population, with a SD of 15. The WMS-R does not provide numerical scores for individuals who score < 50. KE, LJ, EP, GP, and GW were given the WAIS-III rather than the WAIS-R. RB was not given the WMS-R. Age indicates the age of the patient when given the News Events Test. Neurohistological information is available for the first five patients listed. Asterisk indicates a lesion limited to the CA1 field of the hippocampus. H, bilateral damage to the hippocampus with minimal damage to adjacent cortex; MTL, bilateral damage to the hippocampus and parahippocampal gyrus.