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Concurrent Impairments in Sleep and Memory in Amnestic Mild Cognitive Impairment

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Abstract

Whereas patients with Alzheimer's disease (AD) experience difficulties forming and retrieving memories, their memory impairments may also partially reflect an unrecognized dysfunction in sleep-dependent consolidation that normally stabilizes declarative memory storage across cortical areas. Patients with amnestic mild cognitive impairment (aMCI) exhibit circumscribed declarative memory deficits, and many eventually progress to an AD diagnosis. Whether sleep is disrupted in aMCI and whether sleep disruptions contribute to memory impairment is unknown. We measured sleep physiology and memory for two nights and found that aMCI patients had fewer stage-2 spindles than age-matched healthy adults. Furthermore, aMCI patients spent less time in slow-wave sleep and showed lower delta and theta power during sleep compared to controls. Slow-wave and theta activity during sleep appear to reflect important aspects of memory processing, as evening-to-morning change in declarative memory correlated with delta and theta power during intervening sleep in both groups. These results suggest that sleep changes in aMCI patients contribute to memory impairments by interfering with sleep-dependent memory consolidation.

Keywords

Long-term memory; Memory consolidation; Mild cognitive impairment; Slow-wave sleep; Polysomnography; Aging

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INTRODUCTION

Declarative memories concern knowledge of episodes and facts, and generally depend on hippocampal-mediated binding that links memory fragments stored across multiple neocortical zones (Eichenbaum & Cohen, 2001). Declarative memory impairments can result from deficient encoding, storage, retrieval, or some combination. In Alzheimer's disease (AD) and amnestic mild cognitive impairment (aMCI), hippocampal dysfunction and decreased cholinergic innervation substantially contribute to declarative memory impairment (Braak & Braak, 1991; Mesulam, 2004; Mesulam, Shaw, Mash, & Weintraub, 2004; Petersen et al., 2006).

Declarative memories are stabilized for long-term storage through *consolidation*, wherein neocortical connections become strengthened and hippocampal dependence decreases (Paller, 2009; for alternative views concerning episodic memories see Moscovitch, Nadel, Winocur, Gilboa, & Rosenbaum, 2006). Given the hypothesis that sleep facilitates consolidation (Maquet, 2001; Marshall & Born, 2007; Paller, 1997; Stickgold, 2005; Sutherland & Lehmann, 2011), it is plausible that sleep deficiencies in AD and aMCI patients could disrupt consolidation and contribute to patients' memory problems.

Slow-wave sleep (SWS) may be especially pertinent for declarative memory consolidation, owing in part to the low-frequency neuronal oscillations [measured as delta power in electroencephalogram (EEG) recordings] that predominate during this sleep stage and are thought to induce widespread neuronal synchrony that facilitates hippocampal-neocortical interaction (Diekelmann & Born, 2010). SWS-rich retention intervals benefit subsequent declarative memory (Drosopoulos, Wagner, & Born, 2005), as does oscillating transcranial electrical stimulation at slow-wave frequencies (Marshall, Helgadottir, Molle, & Born, 2006; Marshall, Molle, Hallschmid, & Born, 2004). Coherence between hippocampal and neocortical networks increases during SWS (Ji & Wilson, 2007; Sirota, Csicsvari, Buhl, & Buzsaki, 2003), and neuroimaging studies reveal relationships between brain activity during SWS and declarative memory (Chee & Chuah, 2008). Furthermore, observations of EEG power in the delta band during sleep are related to declarative memory assessed before sleep (Bodizs, Bekesy, Szucs, Barsi, & Halasz, 2001; Goder et al., 2006). Notably, during SWS, reactivation of some recently encoded memories is thought to take place, as SWS hippocampal firing patterns parallel those present during waking (Pavlides & Winson, 1989; Wilson & McNaughton, 1994), and reactivating recently learned memories *via* external cues during SWS benefits declarative memory (Rasch, Buchel, Gais, & Born, 2007; Rudoy, Voss, Westerberg, & Paller, 2009).

Declarative memory consolidation may nonetheless depend on sleep mechanisms beyond slow-wave activity. Other results implicate spindle activity (Clemens, Fabo, & Halasz, 2005; Schabus et al., 2004) and theta power that predominates during rapid-eye-movement (REM) sleep (Fogel, Smith, & Cote, 2007; Nishida, Pearsall, Buckner, & Walker, 2009). Also, fluctuating levels of acetylcholine across non-REM and REM sleep may mediate hippocampal-neocortical information exchange and synaptic plasticity (Power, 2004).

Alzheimer's pathology interferes with sleep physiology. Sleep abnormalities typically observed in AD patients include reductions in sleep efficiency, spindle activity, SWS, and REM, along with an increased arousal index (Bliwise, 1993; McCurry & Ancoli-Israel, 2003; Rauchs et al., 2008). Patients with aMCI express subjective sleep complaints (Beaulieu-Bonneau & Hudon, 2009), and in a recent study, such complaints were found to correlate with later memory (Westerberg et al., 2010). However, the extent to which objective neurophysiological sleep parameters are altered in aMCI patients is unknown.

To determine whether sleep physiology is deficient in aMCI and if the degree of these deficiencies is related to degree of declarative memory impairment, we examined memory/sleep relationships in aMCI patients and age- and education-matched cognitively healthy older adults (Table 1). Polysomnographic (PSG) data were acquired during two experimental nights, with memory testing before and after sleep each night (Figure 1). Memory tests included two declarative memory tests (word-pair recall, fact recognition) and a non-declarative memory test (object priming).

METHOD

This study was approved by the Northwestern University Institutional Review Board. We complied with ethical standards of the Declaration of Helsinki.

Participants

Eighteen cognitively healthy older adults and 10 aMCI patients recruited from the Northwestern Alzheimer's Disease Center participated in exchange for monetary compensation. Data from 1 control participant were excluded due to previously undetected sleep apnea, and 1 control and 2 patients elected not to complete the full protocol, resulting in a final group of 16 controls (3 male) and 8 aMCI patients (1 male). Mean age and years of education were matched across control and aMCI groups [age: 72.7 (63.2–79.1; $SD = 5.1$) and 75.6 years (62.3–82.8; $SD = 7.2$), respectively, $p > .3$; education: 15.6 (12–20; $SD = 2.5$) and 14.5 years (10–18; $SD = 3.0$), respectively, $p > .3$].

Participants were clinically evaluated and given a neuropsychological assessment (Table 1). Diagnosis of aMCI followed current guidelines (Petersen, 2004), and reflected scores of 1.5 or more standard deviations below the mean for individuals of comparable age, gender, and education level in one or more cognitive domains including declarative memory, no impairments in daily living activities as assessed with the Functional Assessment Questionnaire (Pfeffer, Kurosaki, Harrah, Chance & Filos, 1982) and the Informant Questionnaire on Cognitive Decline in the Elderly (Jorm, 1994), and failure to reach clinical criteria for dementia. No aMCI patients were taking acetylcholinesterase inhibitors. Exclusion criteria included history of central nervous system disease, major psychiatric disorder, alcohol or substance abuse, serious medical illness (thyroid disorder, renal, hepatic, cardiac, or pulmonary insufficiency, unstable diabetes, uncontrolled hypertension, cancer), chronic use of psychoactive or hypnotic medications, and one or more sleep disorders (uncontrolled sleep apnea, restless leg syndrome, narcolepsy). Three of the 16 controls were not given a full clinical evaluation but had no memory complaints and did not meet any exclusion criteria.

General Procedure

During a preliminary interview, experimental procedures were explained, written consent was obtained, and questionnaires regarding recent sleep habits, sleep quality, and daytime sleepiness were administered (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989; Johns, 1991). No significant group differences were found [sleep habits/quality: $p > .6$; daytime sleepiness: $p > .4$].

At home, participants wore an activity sensor, recorded bed and wake times, and completed questionnaires regarding sleep quality (Akerstedt, Hume, Minors, & Waterhouse, 1994) for 1 week. These data verified that participants adhered to a regular sleep schedule.

Participants spent two experimental nights at the Clinical Research Unit of Northwestern Memorial Hospital. On average, 11 days intervened between the two nights (range: 7–14 days). Participants also underwent an adaptation night that directly preceded the first

experimental night. During the adaptation night, participants were familiarized with procedures and screened for sleep disorders. Data from the adaptation night were not included in any analyses reported here. Each night, the experimental procedures were identical, with the exception that specific stimuli tested were different each night. Preparation for PSG began 3 hrs before regular bedtime. Approximately 1.5 hrs before bedtime, participants completed the Positive and Negative Affectivity Scale (PANAS; Watson, Clark, & Tellegen, 1988), answered the question "How awake do you feel right now?" on a 1–5 scale (1 = very sleepy, 5 = wide awake), and then completed the memory tests. PANAS responses and answers to the sleepiness question did not predict memory, nor were group differences present in these two measures (p values > .1). Lights were turned off according to typical bedtimes for each participant, and participants were allowed to sleep uninterrupted until they woke up for the day on their own or until their typical wake-up time, whichever came first. After waking, participants were given 1 hr to clean up and eat breakfast. Participants then completed a subjective sleep questionnaire, the PANAS, and three memory tests.

Memory Tests

Two declarative memory tests and one nondeclarative memory test were administered in the same order each night. Different sets of stimuli were introduced each night. Each morning, the three memory tests were administered again (without additional encoding), in the same order each morning (Figure 1). Memory scores were computed for each evening and each morning test, and were submitted to across-group comparisons. Change scores for the two declarative memory tests were computed by subtracting each evening score from the corresponding morning score. For the nondeclarative test, evening priming scores were subtracted from morning priming scores. Change scores were then correlated with sleep measures.

Word-pair recall—At encoding, participants studied 44 related word pairs (e.g., story-article), adapted from previous investigations of sleep and memory (Marshall et al., 2004, 2006; Plihal & Born, 1997). Words were presented centrally on a computer screen, one above the other, at a rate of one pair every 4 s. Participants were told to memorize each pair. Next, they completed math problems for 1 min, to minimize word rehearsal. Then, the first word of each pair was presented for 4 s and participants were asked to say the other member of the pair aloud. After 4 s, a tone sounded and the correct answer appeared directly below the first word, and both remained for 4 s. After the last pair, participants completed math problems for 1 min and then took the same test again, to ensure robust learning of the word pairs. Only scores from the second test were used to compute evening memory scores. In the morning, the test was given once more using the same format. Each time the test was given, the same word pairs were presented in a different random order except that the first two and last two pairs studied during encoding were always the first and last two tested, respectively (these trials were excluded from analyses to minimize serial position effects).

Fact recognition—At encoding, participants viewed a set of monochrome facial images (six male, five female). Each face was presented for 15 s above four biographical facts (e.g., Christine/was homeless/won the state lottery/bought a health food store) meant to simulate meeting each person. The first fact was always a name. Then, the screen showed a 5-point rating scale, and participants rated the emotionality of the description (1 = very emotional, 5 = not emotional) to ensure they were encoding the descriptions. After 11 encoding trials, participants solved math problems for 1 min. Then, 10 test trials began using all the studied stimuli except the first studied face and associated facts. On the first trial, 1 face appeared on the left and 10 names on the right. Participants were asked to press the number corresponding to the correct name. If they did not know the correct name, they were asked

to guess. After a button was pressed, a list of 10 facts appeared on the right, and participants attempted to press the number corresponding to the correct fact. This procedure continued for the final two facts, and then a new face appeared on the left side and the testing process repeated for the remaining nine faces. Following the evening test, each face and associated facts were presented for 15 s each, providing an additional learning opportunity. No additional testing was completed in the evening. The morning test was otherwise identical to the evening test. Across the evening and morning tests, faces, and facts appeared in a different random order. Within each test, the facts were presented in the same order for each of the 10 trials.

Object priming—At encoding, participants viewed 30 color pictures of common objects for 4 s each. Participants were asked to say aloud the name of each object as soon as it appeared. Immediately following each object presentation, a rating scale appeared and participants were asked to rate how much they liked each object (1 = like very much, 4 = dislike very much). Participants were not informed that memory for these objects would be subsequently tested, nor were they informed when tested that any previously seen objects would be used. At test, the same 30 objects were randomly intermixed with 30 new objects, each flashed for 102 ms followed by a mask for 102 ms. Participants pressed “b” if they recognized the identity of the object and “n” if not, and if they pressed “b” they named the object aloud as quickly and accurately as possible. A “b” press was only counted as correct if the spoken object name was accurate. The morning test was the same except there was a different set of 30 new objects and a different random order. The percent of new objects correctly recognized was subtracted from the percent of old objects correctly recognized to obtain a priming score for each test.

PSG recording and analyses

Sleep EEG was measured using electrodes placed at eight sites from the 10-20 system (C3, C4, O1, O2, F3, F4, P3, and P4), referenced to average mastoids, along with electrooculogram, chin electromyogram, and electrocardiogram channels. For three aMCI patients and two controls, electrodes were placed only at C3, C4, O1, and O2 due to recording limitations. On the adaptation night, nasal/oral airflow, abdominal and chest respiration, pulse oximetry, and leg electromyogram were also monitored. Signals were sampled at 200 Hz (Neurofax EEG-1100, Nihon Khoden) and amplified using a 0.27- to 70-Hz bandpass filter. Sleep staging was accomplished using standard criteria (Iber, Ancoli-Israel, Chesson, & Quan, 2007).

EEG spectral analyses were conducted following artifact removal based on visual inspection. Fast Fourier transform was applied using a Hanning function and 4-s intervals with 50% overlap, yielding a frequency resolution of 0.25 Hz. Estimates were averaged for 30-s epochs aligned with sleep stages and absolute power computed for delta (0.5–4.5 Hz), theta (4.5–8.5 Hz), alpha (8.5–12.5 Hz), and sigma (12.5–15.5 Hz) frequency bands. Reported EEG power values were averaged across the four electrode locations recorded in all participants unless otherwise stated.

Sleep spindles in the frequency range from 12.5–15.5 Hz were detected automatically at each electrode (amplitude > 12 μV; duration 0.5–3.0 s). Fast (13–15 Hz) and slow (11–13 Hz) spindles were also detected with the same criteria. Scoring, artifact rejection, spectral analyses, and spindle detection were completed with Prana software (Phitools).

RESULTS

Memory Dysfunction in aMCI

For each test type, performance was averaged across the two evening sessions to yield an evening memory score, as preliminary analyses indicated no significant differences between night 1 and night 2 evening scores. Likewise, performance was averaged across the two morning sessions to yield a morning memory score, as preliminary analyses indicated no significant differences between the two morning scores. To compare memory performance across groups, a 2 × 2 analysis of variance (ANOVA) with test time (evening, morning) as the within-subjects variable and group (control, aMCI) as the between-subjects variable was used to assess test performance. A Bennett-Box test conducted with each ANOVA ensured homogeneity in across-group variance for all three tests (p values > .2). Results from all tests are depicted in Figure 2.

Word-pair recall—Recall scores from the second test each evening were entered into the ANOVA to assess performance. Recall was better in the control group than in the aMCI group (66% and 32%, respectively), as shown by a significant main effect of group [$F(1,22) = 15.6$; $p < .001$]. The test time × group interaction was also significant [$F(1,22) = 9.6$; $p < .01$]. Controls improved their recall in the morning relative to that in the evening [$t(15) = 2.2$; $p < .05$], whereas aMCI patients did not, instead recalling less in the morning compared to the evening [$t(7) = 3.4$; $p < .05$]. The main effect of test time was not significant ($p > .9$).

To determine whether immediate feedback given to participants on each trial of this test was differentially effective at improving memory across aMCI and control groups, evening recall improvement scores were calculated by subtracting performance on the first evening recall test from performance on the second evening recall test for each night. Evening recall improvement scores did not significantly differ between groups [night 1: $t(23) = 1.7$; $p > .05$; night 2: $t(23) = 1.7$; $p < .05$].

Fact recognition—Recognition was better in controls than in aMCI patients (56% and 23%, respectively), as shown by a main effect of group [$F(1,22) = 17.3$; $p < .001$]. The test time × group interaction was marginal [$F(1,22) = 3.8$; $p < .07$]; controls improved their scores in the morning relative to the evening [$t(15) = 2.9$; $p < .05$] whereas aMCI patients did not ($p > .8$). The main effect of test time was not significant ($p > .1$).

Object priming—Priming scores were computed as the difference in naming accuracy between old and new objects. Priming magnitude was nearly identical in the control and aMCI groups (21% and 22%, respectively). The main effect of group was not significant ($p > .9$), but the main effect of test time was [$F(1,22) = 10.0$; $p < .005$]. Priming was stronger on the evening test (25%) than on the morning test (18%), presumably because of the shorter delay from encoding. The test time × group interaction was not significant ($p > .5$).

Sleep disruptions in aMCI

Measures computed for each participant did not significantly differ across nights. Accordingly, to compare potential differences in sleep across groups, sleep latency, total sleep time, minutes in each stage (and corresponding percentages spent in each stage relative to total sleep time), minutes of wake-after sleep onset (WASO), REM latency, and sleep efficiency (total sleep time divided by total recording time) were averaged across nights. Large group differences were present in SWS and modest group differences were present in other measures (Table 2). The aMCI group spent fewer minutes in SWS [$t(22) = 2.8$; $p < .05$], with a correspondingly lower SWS percentage than in the control group [$t(22) = 2.7$; $p < .05$]. Marginal group differences were present in REM minutes [$t(22) = 2.0$; $p < .07$],

REM percentage [$t(22) = 2.1$; $p < .06$], WASO minutes [$t(22) = 1.8$; $p < .08$], WASO percentage [$t(22) = 2.0$; $p < .06$], REM latency [$t(22) = 2.0$; $p < .07$], and sleep efficiency [$t(22) = 2.0$; $p < .06$].

To determine whether the magnitude of aMCI disruption relative to controls differed between SWS and REM, as has been suggested for healthy older *versus* younger adults (Van Cauter, Leproult, & Plat, 2000), a ratio of SWS min to REM min was computed for each participant. These ratios were significantly smaller for aMCI patients than for controls [.007 *vs.* .12, respectively; $t(22) = 2.6$; $p < .05$]. Although all participants spent more time in REM than SWS, by this metric, the amount of SWS relative to REM is smaller in aMCI patients compared with controls, highlighting the disproportionate SWS disruption in aMCI.

EEG power averaged across non-REM (stages 1, 2, and SWS) and REM sleep periods for the two nights also revealed reliable group differences. Table 3 shows power values and results from across-group *t*-tests at each recording location for non-REM and REM sleep periods. During non-REM, delta and theta were reduced in aMCI patients compared to controls [$t(22) = 2.3$; $p < .05$, and $t(22) = 2.2$; $p < .05$, respectively]. These differences remained present when stage 2 was examined alone [delta: $t(22) = 2.1$; $p < .05$; theta: $t(22) = 2.2$; $p < .05$], reflecting the large contribution of stage-2 to the non-REM category. During REM, the aMCI group also showed a significant reduction in theta [$t(22) = 2.9$; $p < .05$], but not in delta [$t(22) = 1.8$; $p < .09$]. Alpha and sigma power did not differ between groups during non-REM or REM periods (p values > .4).

Spindle counts focused on frontal and parietal locations during stage 2 for all participants with data from these recording sites ($n = 5$ aMCI patients, $n = 13$ controls), given prior reports that spindle activity is maximal at these locations and during this stage (Zygierewicz et al., 1999). Spindle counts were reduced in aMCI patients at F3 and F4 recording sites compared to controls [F3: aMCI average = 86, control average = 318; $t(17) = 2.9$; $p < .01$; F4: aMCI average = 85; control average = 331; $t(17) = 3.1$; $p < .01$], but not at parietal sites (p values > .7). Consistent with evidence that fast spindles may be more affected by AD pathology than slow spindles (Rauchs et al., 2008), stage-2 frontal reductions in the aMCI group were present in fast spindles but not in slow spindles [F3: $t(17) = 2.8$; $p < .05$; F4: $t(17) = 2.9$; $p < .05$].

Declarative memory retention is related to physiological aspects of sleep

Further analyses were undertaken to isolate aspects of sleep physiology contributing to memory consolidation. Memory change scores were correlated separately with delta power, theta power, and stage-2 spindle counts from frontal electrodes from the intervening night, as previous studies have reported relationships between memory and these aspects of sleep in younger adults. Although SWS has also been implicated in consolidation, the lack of SWS in nine of our participants precluded correlation analyses with this variable. Initial analyses included all participants, and for each, EEG power values were computed during sleep across the whole night. Correlations were computed separately for each of the two nights.

On night 1, word-pair recall change scores were predicted by delta ($r = .55$; $p < .01$) and theta ($r = .52$; $p < .01$), but not frontal stage-2 spindles (p values > .1). Increases in both delta and theta power were associated with positive change scores, as depicted in Figure 3. These correlations were likely not attributable to type I errors, as both correlations were significant at a stringent $p < .01$ level. Additional analyses showed that these correlations were also present when EEG power was computed separately for non-REM and REM sleep periods, and when each group was examined separately (Table 4). Correlation coefficients

were very similar across the two groups, though in the aMCI group alone they were not significant, likely due to the small size of that group.

On night 2, a similar pattern of results was observed. Word-pair recall scores were positively correlated with theta ($r = .59$; $p < .01$) and marginally positively correlated with delta ($r = .41$; $p < .08$), but not with frontal stage-2 spindle counts (p values > .2). Correlations with delta and theta were also significant when non-REM and REM sleep periods were analyzed separately. When each group was examined separately, correlation coefficients just failed to reach significance (p values < .1) but reflected the same patterns as when both groups were examined together. See Table 4 for correlation coefficients for all analyses.

Connections between sleep and either biographical fact recognition or nondeclarative memory were less clear-cut. Correlation analyses did not reveal any significant relations between these memory tests and sleep parameters.

Sleep may also benefit memory by increasing morning alertness. However, if alertness or other nonspecific factors contributed to the correlations reported above, then one might expect sleep quality to predict response time in the morning. Response time to make a recognition decision on the object-priming test was measured for all objects. Yet, response-time decrease from evening to morning (58 ms and 162 ms for MCI patients and controls, respectively) was not correlated with any sleep parameter (rs < .2).

DISCUSSION

Whereas disruptions of sleep physiology have previously been observed in AD, the present results are, to our knowledge, the first to demonstrate physiological abnormalities in aMCI patients. In comparisons with healthy individuals matched on age and education, differences were prominent in delta and theta power and in SWS. Importantly, aspects of sleep disrupted in aMCI were also implicated in declarative memory consolidation, suggesting that sleep disruptions in aMCI can thwart overnight consolidation and thus contribute to memory deficits that these patients experience.

SWS was dramatically reduced in aMCI patients, in tandem with borderline changes in REM, WASO, REM latency, and sleep efficiency. These differences are consistent with reports in AD (Bliwise, 1993; McCurry & Ancoli-Israel, 2003) and suggest that alterations in sleep physiology beyond what occurs in healthy aging could signal neurodegenerative pathology. The finding that group differences were greater in SWS than in REM parallels findings in healthy aging (Benca, Obermeyer, Thisted, & Gillin, 1992; Ehlers & Kupfer, 1989; Van Cauter et al., 2000). We thus speculate that SWS begins to decline in healthy aging and then declines further in aMCI, whereas in advanced stages of AD, REM decline accelerates such that SWS no longer stands out as a selectively targeted sleep stage (Prinz, Poceta, & McCurry, 2002).

Sleep spindles, typically maximal during stage 2, have also been implicated in consolidation (Clemens et al., 2005; Schabus et al., 2004, 2008; Tamaki, Matsuoka, Nittono, & Hori, 2008). Here, reduced stage-2 spindle counts at frontal recording sites in aMCI patients are consistent with reports of reduced spindle activity in AD (Bliwise 1993; McCurry & Ancoli-Israel, 2003; Rauchs et al., 2008). Our finding that fast but not slow spindles showed reductions is also in keeping with evidence that fast spindles (typically 13–15 Hz) are most disrupted in AD (Rauchs et al., 2008).

In some ways, however, the findings in aMCI diverged sharply from what is typically found in AD. In particular, aMCI patients exhibited substantial reductions in delta and theta, whereas AD patients can show faster mean theta frequencies (Hot et al., 2011) and often

show an overall shift to predominantly delta and theta both during sleep and during wakefulness (Bliwise, 1993; Petit, Montplaisir, Lorrain, & Gauthier, 1992; Prinz, Larsen, Moe, & Vitiello, 1992). Yet, levels of delta and theta during sleep are typically diminished in older adults relative to younger adults (Ehlers & Kupfer, 1989; Landolt & Borbely, 2001).

Importantly, our correlational results provided a key insight into the functional repercussions of reduced delta and theta power. Not only were these two measures reduced in aMCI patients compared to controls, but these measures were also the most severely reduced for those individuals who gained the least overnight benefit, or obtained no overnight benefit, in word-pair recall (Figure 3). These results are not easily attributable to a nonspecific benefit of sleep, such as increased alertness, because these two sleep parameters correlated with changes in recall but not with changes in recognition, priming, or response speed. Likewise, these correlations did not arise merely because the two groups differed in both EEG and recall measures. When correlations were examined for each group separately, controls and aMCI patients showed the same general pattern of associations. Although relationships did not reach statistical significance in all conditions when the modestly sized groups were examined separately, correlation coefficients were similar across the two groups and these values were similar to those from the combined sample. Presumably, this pattern of results indicates that these relationships hold regardless of neuro-pathology. Delta and theta power thus appear to index processes related to the overnight stabilization of memory storage that involves hippocampal binding and facilitates later recall.

Of course, factors beyond sleep-dependent consolidation likely contributed to overnight changes in memory. For example, circadian effects likely influenced performance on the evening and morning tests (Hogan et al., 2009). Also, similar memory changes might have occurred during an 8-hr delay during the day. Whether or not such memory changes occur during the day, the most important conclusions are based on the correlations with delta/theta, which suggest that memory processing during sleep is relevant for these memory changes, consistent with the speculation that poor sleep contributes to poor memory in MCI.

Thus, the neuropathology in aMCI not only produces dysfunction at the moment of memory acquisition, but it seems to disrupt delta and theta activity along with memory reactivation and stabilization during sleep. Word-pair recall performance also supports this conclusion, as recall was superior in the morning compared to the prior evening in controls, whereas recall declined overnight in the aMCI group, suggesting that sleep-dependent consolidation processes were more effective in controls. We cannot rule out a contribution from circadian factors to the differential overnight memory change. Recall feedback might also have been relevant if it was more effective in controls than in aMCI patients. This is unlikely, however, as an analysis of memory improvement from first to second evening test yielded no evidence for differential benefit from feedback between the groups. Still, differences could emerge at longer delays. Despite these complexities, the different patterns of overnight memory change in the two groups remain an interesting topic for future investigation.

Delta power during sleep has been associated with the consolidation of many types of memory (Bodizs et al., 2001; Goder et al., 2006; Huber, Ghilardi, Massimini, & Tononi, 2004; Wamsley, Tucker, Payne, & Stickgold, 2010). In particular, overnight improvement in nondeclarative memory and in maze navigation learning have been associated with delta from the intervening night. In studies that tested declarative memory *via* recall or recognition (Bodizs et al., 2001; Goder et al., 2006), delta was related to memory that was assessed before sleep, but overnight change in memory was not evaluated. Our results support and extend these findings, as here we demonstrated a relationship between delta and overnight memory change, which more strongly implicates delta in memory consolidation. This emphasis on delta activity is consistent with theories positing that during SWS, when

delta is most predominant, consolidation of recently acquired information is accomplished *via* neural changes resulting from interactions between hippocampal and neocortical networks (Diekelmann & Born, 2010). The persistence of delta correlations during REM suggests that even low levels of slow-wave activity can influence memory processing. REM delta could reflect the persistence of hippocampal/neocortical interactions from non-REM sleep, or other processes (e.g., hippocampal plasticity). Relationships between REM and declarative memory consolidation have been previously reported (Bodizs et al., 2001; Rauchs et al., 2004), and are in agreement with theories positing neural processes contributing to declarative memory consolidation likely occur across multiple sleep stages (e.g., Diekelmann & Born, 2010).

Time spent in SWS each night, defined by conventional sleep-staging methods, declines considerably in aging (Bliwise, 1993; Danker-Hopfe et al., 2005; Van Cauter et al., 2000). In two controls and in five aMCI patients, no epochs of SWS were observed across both nights. Notably, conventional sleep staging methods are insensitive to low levels of slow-wave activity, as slow-wave amplitudes must be greater than 75 microvolts to count as SWS. On the other hand, delta power (slow-wave activity computed in the delta band) provides a more fine-grained measure across the whole night, especially in individuals with lower-amplitude slow waves. Accordingly, correlational analyses of memory decline in aging and aMCI can be more powerful when using delta power than amount of SWS, and here this approach allowed us to link slow-wave activity with memory consolidation. Future research in populations with diminished SWS levels may benefit from comparable analyses.

Relationships between overnight recall change and theta were also observed. These findings are consistent with recent results showing a positive relationship between theta during SWS and delayed recall in AD patients (Hot et al., 2011). Two other studies implicated theta during REM in declarative memory consolidation (Fogel et al., 2007; Nishida et al., 2009). Here, recall was related to theta across all sleep periods, as well as during REM and non-REM analyzed separately. Hippocampal theta is prominent during REM, and is hypothesized to reflect synchronization of neuron ensembles within different hippocampal subunits and limbic structures in the service of synaptic plasticity (Buzsaki, 2002; Montgomery, Sirota, & Buzsaki, 2008). Theta during waking has also been associated with declarative memory (Klimesch, Doppelmayr, Russegger, & Pachinger, 1996; Weiss & Rappelsberger, 2000), and intracranial EEG recordings suggest that wake theta shares the same neural generators as those observed during REM sleep (Babiloni et al., 2009). Yet, the extent to which scalp EEG theta during sleep is influenced by hippocampal theta rhythms is unknown. Thus, future investigations are necessary to determine how hippocampal theta may contribute to theta recorded at the scalp and whether REM and non-REM theta reflect similar neurophysiological events relevant for consolidation.

The current investigation included two tests of declarative memory, a word-pair recall test and a fact recognition test. Connections between sleep and consolidation were found only for recall. There are multiple reasons why recognition may not be as sensitive as recall in detecting sleep/memory relationships. First, recall places more demands on producing information from memory, whereas recognition is accomplished by selecting information from a set of choices. Consolidation may aid the strategic retrieval required for recall more than the potentially less extensive retrieval that can support recognition. Lower mean accuracy for recognition (44% correct) compared to recall (55% correct) may also be relevant. Correct answers *via* guessing were more likely for recognition, especially as some choices could often be eliminated based on prior trials. Also, for biographical facts that were not well learned, less benefit may have accrued from sleep-dependent consolidation because memory storage was too weak (Stickgold, 2009). Another factor that may be relevant pertains to the types of associations formed. The two memory tests relied on different sorts

of associations, which can be relevant for which brain areas are involved in storage (Mayes, Montaldi, & Migo, 2007), and can impact sleep/memory relationships (Schmidt et al., 2006). At any rate, word-pair recall not only provided evidence in support of sleep/memory relationships here, but has also been used in other experiments implicating sleep in the consolidation of declarative memories (Fogel et al., 2007; Marshall et al., 2004, 2006).

The present study characterizes physiological sleep abnormalities in aMCI for the first time, and correlational data supported the hypothesis that sleep is involved in memory processing. Future research exploring the effects of direct manipulations of sleep on memory will further understanding of how memories are processed during sleep (Marshall et al., 2004, 2006; Rasch et al., 2007; Rudoy et al., 2009). A thorough understanding of sleep/memory relationships and changes in these relationships in aMCI patients can help reveal how remembering a lifetime of memories depends not only on information acquisition and retrieval, but also on intervening consolidation during sleep. Disrupted memory processing during sleep may contribute to memory problems in neurodegenerative diseases and in aging generally. Further efforts in this vein could lead to sleep-focused treatments designed to offset cognitive decline. The present results provide evidence that neural dysfunction in aMCI hinders some aspects of sleep, and that these same aspects of sleep are important for memory consolidation, supporting the conclusion that the memory problems these patients experience partially reflect deficient information processing during sleep. The delta and theta reductions in aMCI—and their connection with declarative memory—indicate that these specific aspects of sleep impact memory consolidation.

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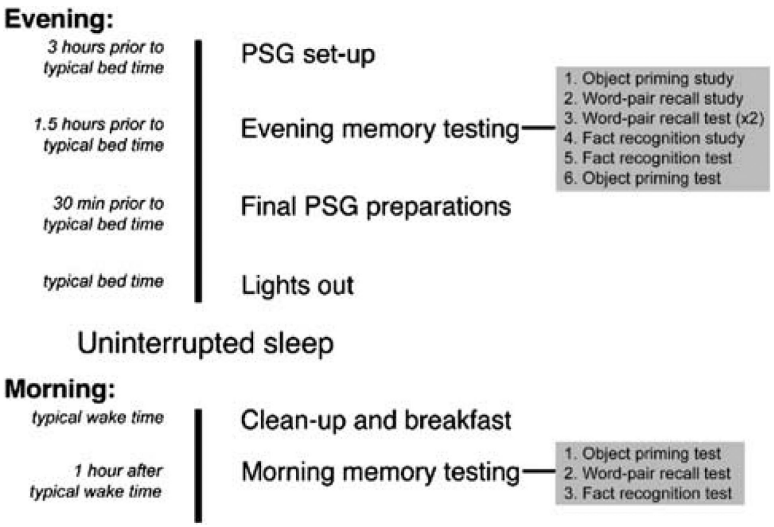

Fig. 1.
Timeline of events for each of the polysomnographic recording nights.

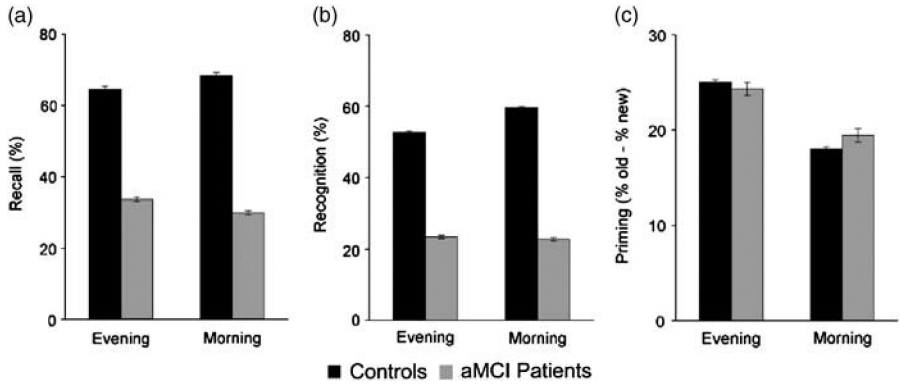

Fig. 2.

(a) Word-pair recall, (b) fact recognition, and (c) priming accuracy for evening and morning test sessions averaged across the two nights for control (n = 16) and aMCI (n = 8) groups.

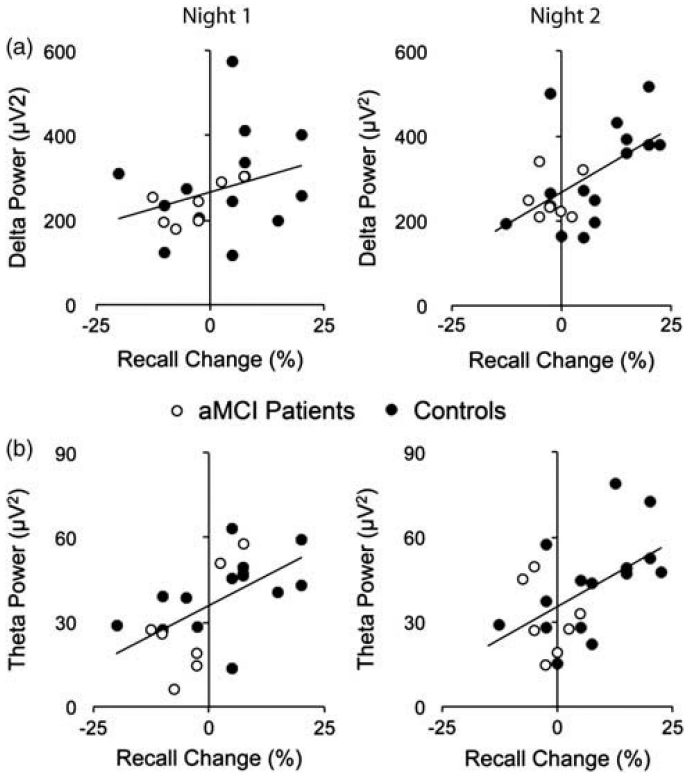

Fig. 3.

(a) Delta power and (b) theta power were positively related to memory change in word-pair recall from evening to morning [$r(22)$, $p < .05$].

Table 1

Neuropsychological testing results for the two groups (with SE in parentheses)

	Maximum score	Controls (*n* = 16)	aMCI patients (*n* = 8)
Mini Mental State Examination (Folstein, Folstein, & McHugh, 1975)	30	28.4 (0.4)	27.3 (0.6)
CERAD category fluency (Morris et al., 1989)	none	22.5 (1.3)	19.8 (2.0)
Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983)	30	29.3 (0.4)	27.0 (1.0)
*Trail Making A (Reitan, 1992)	150 s	27.5 (2.6)	47.6 (5.0)
Trail Making B (Reitan, 1992)	300 s	72.9 (10.4)	121.8 (28.1)
WMS-R digit span-forward (Wechsler, 1987)	12	7.6 (0.5)	7.0 (0.9)
WMS-R digit span-backward (Wechsler, 1987)	12	6.3 (0.3)	4.8 (1.4)
WAIS-R digit symbol (Wechsler, 1987)	93	47.0 (2.0)	39.4 (4.5)
*WMS-R logical memory Story A I (Wechsler, 1987)	25	14.6 (1.0)	9.9 (1.4)
*WMS-R logical memory Story A II (Wechsler, 1987)	25	14.0 (1.2)	7.9 (1.6)
*RAVLT immediate memory (Rey, 1970)	15	10.2 (1.0)	5.9 (1.3)
*RAVLT delayed memory (Rey, 1970)	15	9.8 (1.1)	4.9 (1.2)
*RAVLT recognition (Rey, 1970)	30	28.1 (0.5)	24.6 (1.2)

Note. CERAD = Consortium to Establish a Registry for Alzheimer's Disease; WAIS-R = Wechsler Adult Intelligence Scale-Revised; WMS-R = Wechsler Memory Scale-Revised; RAVLT = Rey Auditory Verbal Learning Test; aMCI = amnestic mild cognitive impairment.

*aMCI patients significantly worse than controls [$t(23)$, $p < .05$].

Table 2

Sleep parameters averaged across the two nights for the two groups (with SE in parentheses)

	Controls (n = 16)	aMCI patients (n = 8)
Stage 1 (min)	25.9 (3.7)	25.0 (3.9)
Stage 2 (min)	225.7 (9.6)	218.8 (15.5)
**SWS (min)	10.2 (3.2)	0.67 (0.6)
*REM (min)	100.2 (6.2)	78.1 (8.9)
*WASO (min)	60.9 (6.9)	95.0 (16.0)
Total sleep time (min)	362.1 (12.0)	322.6 (20.6)
Sleep latency (min)	17.1 (3.9)	22.3 (6.8)
Time in bed (min)	410.6 (20.3)	414.1 (32.5)
*REM latency (min)	68.9 (4.9)	124.3 (24.7)
*Sleep efficiency (%)	85.8 (1.4)	77.2 (3.7)
Stage 1 (%)	6.2 (0.9)	6.2 (1.0)
Stage 2 (%)	52.5 (1.7)	50.9 (2.5)
**SWS (%)	2.7 (0.9)	0.2 (0.1)
*REM (%)	23.7 (1.1)	18.8 (2.0)
*WASO (%)	14.3 (1.4)	22.8 (3.7)

Note. SWS = slow-wave sleep; REM = rapid eye movement; WASO = wake after sleep onset; aMCI = amnestic mild cognitive impairment. Percent measures are in relation to sum of total sleep time and WASO.

** aMCI group significantly less than the control group [$t(23)$, $p < .05$].

* aMCI group marginally different from the control group [$t(23)$, $p < .08$].

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Table 3

Average absolute power (μV^2) for non-REM and REM sleep periods averaged across the two nights at individual electrode sites in the delta, theta, alpha, and sigma bands (with SE in parentheses)

	C3	C4	O1	O2	F3	F4	P3	P4
Non-REM delta								
Control	492 (43)	540 (47)	242 (27)	264 (30)	446 (41)	502 (54)	367 (36)	409 (41)
aMCI	383 (35)	387 (42)	186 (12)	212 (48)	335 (86)	356 (84)	239 (25)	244 (29)
t value	1.93	2.35	1.85	1.48	1.09	1.37	2.86	3.20
p value	.07	.03	.08	.15	.29	.19	.01	.01
REM delta								
Control	150 (12)	161 (13)	82 (11)	86 (12)	131 (18)	159 (20)	116 (12)	124 (13)
aMCI	125 (14)	124 (12)	65 (8.3)	73 (8.2)	137 (23)	142 (15)	121 (32)	120 (36)
t value	1.35	2.08	1.19	0.83	0.18	0.64	0.14	0.12
p value	.19	.05	.25	.42	.86	.53	.89	.90
Non-REM theta								
Control	56 (6.0)	62 (6.3)	39 (4.5)	43 (5.2)	33 (4.5)	45 (6.0)	48 (5.5)	53 (5.4)
aMCI	35 (6.8)	38 (7.5)	26 (5.0)	30 (6.2)	21 (5.0)	23 (5.1)	24 (3.4)	26 (4.2)
t value	2.25	2.46	1.87	1.63	1.75	2.73	3.71	3.86
p value	.03	.02	.07	.12	.10	.01	.002	.001
REM theta								
Control	38 (4.6)	42 (5.0)	23 (3.4)	26 (4.1)	22 (2.9)	27 (3.6)	32 (4.1)	35 (4.4)
aMCI	20 (2.9)	23 (3.5)	14 (2.6)	16 (3.0)	15 (4.3)	15 (3.8)	15 (3.5)	16 (3.6)
t value	3.28	3.08	2.11	1.92	1.37	2.13	2.88	3.09
p value	.003	.006	.05	.07	.19	.04	.01	.01
Non-REM alpha								
Control	28 (4.1)	31(4.3)	14 (2.6)	16 (2.9)	16 (2.2)	22 (3.0)	21 (3.4)	23 (3.2)
aMCI	35 (11)	37 (12)	15 (4.0)	16 (3.8)	30 (19)	32 (20)	41 (28)	43 (29)
t value	0.52	0.42	0.04	0.15	0.65	0.48	0.66	0.64
p value	.61	.68	.97	.88	.52	.64	.52	.53
REM alpha								
Control	18 (3.0)	20 (3.2)	14 (2.9)	16 (3.5)	11 (1.7)	14 (2.1)	18 (2.8)	20 (3.2)
aMCI	17 (3.2)	18 (3.2)	10 (2.3)	12 (2.4)	12 (3.9)	14 (4.8)	16 (5.6)	17 (5.6)

	C3	C4	O1	O2	F3	F4	P3	P4
t value	0.40	0.32	1.00	1.05	0.21	0.01	0.27	0.40
p value	.69	.75	.33	.31	.84	.99	.79	.69
Non-REM sigma								
Control	10 (3.6)	10 (4.1)	5.0 (2.3)	5.5 (2.9)	4.1 (2.1)	5.6 (3.3)	8.9 (3.5)	10 (4.2)
aMCI	9.3 (1.5)	9.5 (1.6)	5.9 (1.4)	6.3 (1.4)	3.4 (0.3)	3.7 (0.3)	6.0 (0.8)	6.4 (1.1)
t value	0.20	0.49	0.55	0.55	1.14	1.97	2.25	2.08
p value	.84	.63	.59	.59	.27	.07	.04	.05
REM sigma								
Control	6.5 (0.7)	6.9 (0.8)	4.0 (0.6)	4.6 (0.8)	3.5 (0.5)	4.4 (0.6)	6.1 (0.7)	6.7 (0.9)
aMCI	7.5 (1.8)	7.8 (1.7)	5.3 (1.5)	5.7 (1.6)	3.3 (0.3)	3.6 (0.3)	5.2 (0.8)	5.1 (0.8)
t value	.51	.45	0.80	0.64	0.37	1.01	0.85	1.32
p value	.61	.66	.43	.53	.71	.32	.40	.20

Note. REM = rapid eye movement; aMCI = amnestic mild cognitive impairment. Averages for C3, C4, O1, O2 sites include $n = 16$ controls, $n = 8$ aMCI patients (df for t-tests = 23; averages for F3, F4, P3, P4 sites include $n = 14$ controls, $n = 5$ aMCI patients (df for t-tests = 18).

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Table 4

Pearson correlation coefficients for recall correlations with delta and theta power

	Both groups, Non-REM	Both groups, REM	Control group	aMCI group
Night 1				
Delta	.51**	.56***	.54*	.46
Theta	.49**	.60***	.55*	.74
Night 2				
Delta	.45**	.51**	.33	.68
Theta	.53***	.68***	.51	.69

Note. REM = rapid eye movement; aMCI = amnestic mild cognitive impairment.

*** $t(22)$, $p < .01$

** $t(22)$, $p < .05$

* $t(14)$, $p < .05$.