ORIGINAL ARTICLE

Sleep Influences the Severity of Memory Disruption in Amnestic Mild Cognitive Impairment

Results From Sleep Self-assessment and Continuous Activity Monitoring

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Abstract: Sleep is important for declarative memory consolidation in healthy adults. Sleep disruptions are typical in Alzheimer disease, but whether they contribute to memory impairment is unknown. Sleep has not been formally examined in amnestic mild cognitive impairment (aMCI), which is characterized by declarative-memory deficits without dementia and can signify prodromal Alzheimer disease. We studied 10 aMCI patients and 10 controls over 2 weeks using daily sleep surveys, wrist-worn activity sensors, and daily recognition tests. Recognition was impaired and more variable in aMCI patients, whereas sleep was similar across groups. However, lower recognition of items learned the previous day was associated with lower subjective sleep quality in aMCI patients. This correlation was not present for information learned the same day and thus did not reflect nonspecific effects of poor sleep on memory. These results indicate that inadequate memory consolidation in aMCI patients is related to declines in subjective sleep indices. Furthermore, participants with greater across-night sleep variability exhibited lower scores on a standardized recall test taken prior to the 2-week protocol, suggesting that consistent sleep across nights also contributes to successful memory. Physiological analyses are needed to further specify which aspects of sleep in neurological disorders impact memory function and consolidation.

Key Words: declarative memory, sleep, amnestic mild cognitive impairment, memory consolidation

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Memories for facts and episodes, known as declarative memories, have long been hypothesized to benefit from processing during sleep.[1,2] Thus, poor sleep has the potential to contribute to memory impairment. Understanding how sleep abnormalities may relate to memory requires the simultaneous examination of sleep and memory, which has seldom been accomplished in neurological disease.

Current theories of declarative memory posit that the hippocampus binds together information represented across various neocortical areas into a coherent memory.[3] Furthermore, newly formed memories are transformed to a more enduring state by undergoing a cross-cortical consolidation process, whereby new memories become integrated with existing traces in the neocortex.[4] This is accomplished through a dialogue between hippocampal and neocortical areas, resulting in strengthened connections between neocortical areas and a decreased dependence on hippocampal binding.[5]

Abundant evidence now suggests that sleep is important for memory consolidation. In rodents, similar hippocampal activity occurs during learning and during subsequent sleep,[6,7] along with signs of hippocampal-neocortical synchrony during sleep.[8,9] In humans, memory enhancements are found following sleep relative to comparable periods of wakefulness.[10] In particular, slow-wave sleep (SWS) has been repeatedly implicated in declarative memory consolidation.[11–13]

With aging, several aspects of sleep typically decline. Older adults take longer to fall asleep, show decreased sleep efficiency, increased wake time after sleep onset, and decreased levels of SWS compared with younger adults.[14] Accordingly, poor sleep in older adults could lead to consolidation deficits that contribute to memory decline. Indeed, SWS reductions are related to minor declines in declarative-memory consolidation in adults aged 48 to 55 years.[15] Although connections between disrupted sleep and disrupted cognition have been observed in adults over age 55 years,[16,17] sleep-memory connections in older adults have received little attention.[18]

Patients with Alzheimer disease (AD) often exhibit dramatic sleep disruptions, and the severity of sleep disruption correlates with dementia severity.[19] In AD, sleep/wake rhythms can become fragmented with periods of waking and sleeping throughout the night and day, and overall sleep levels are reduced.[20] Amnestic mild cognitive impairment (aMCI) denotes a stage intermediate between healthy aging and AD.[21,22] Individuals with aMCI exhibit memory impairments larger than expected for their age and education level, with preserved abilities in daily living

activities. Some MCI patients exhibit primary deficits in other cognitive domains; here we focus only on the amnestic subtype.

Although sleep has not been systematically examined in aMCI, sleep disruptions are frequently reported by patients and their caregivers.[23] Thus, in aMCI and perhaps other neurological disorders, disrupted sleep may contribute to memory dysfunction. Memory problems in AD and aMCI patients arise primarily from neuropathology in medial temporal regions. The hippocampus is the first and most extensively affected region.[24,25] Hippocampal insult could hinder consolidation by compromising cross-talk between hippocampus and neocortex. Recent neuroimaging studies indicate that some memories may be redistributed to prefrontal cortex during sleep-dependent consolidation.[26–28] Thus, prefrontal dysfunction present in AD[29] and aMCI[30] may also be relevant for consolidation.

We investigated memory and sleep in aMCI patients and cognitively typical older adults using a 2-week protocol administered in their homes. Memory was measured with daily recognition tests that could be completed reliably without an experimenter present. Sleep was monitored with daily questionnaires and with actigraphy, which provides sleep-pattern assessment via a wrist-worn movement sensor and has been validated against physiological data.[31] Unlike polysomnography (PSG), actigraphy allows for unobtrusive data acquisition in a home environment for many consecutive nights.

Our central goal was to determine the extent to which daily variations in memory may be related to daily variations in sleep. Given that disease-related changes in sleep may alter consolidation during sleep, relationships between daily sleep and memory measures might be apparent in aMCI patients. We also investigated whether sleep variability was meaningfully related to memory.

METHODS

Protocol Approvals

This protocol was approved by the Northwestern University Institutional Review Board. Written informed consent was obtained from all participants.

Participants

Ten aMCI patients (8 female) and 10 controls (7 female) were recruited from the Memory Disorders Research Core registry of the Cognitive Neurology and Alzheimer Disease Center at Northwestern University. The mean ages were 71.1 and 72.5 years, and the mean education levels were 13.1 and 15.1 years, for the aMCI and control groups, respectively. Neither age nor education level differed significantly between groups (*t*-test *P* values > 0.16).

All participants underwent clinical evaluation including a neuropsychological test battery. Tests included Mini-Mental State Evaluation[32] (global cognitive function), Trail Making A and B[33] (executive function), Boston Naming Test[34] (language), Word List Learning and Recognition (declarative memory), Constructions (visuospatial function), and Category Fluency (semantic memory, attention) subtests of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery,[35] and Logical Memory and Visual Reproduction subtests of the Wechsler Memory Scale-Revised[36] (WMS-R; declarative memory). Subtest I of each scale tests immediate memory, whereas subtest II tests short-delay memory. Table 1 shows scores

from a subset of these tests. Participants also completed the Functional Assessment Questionnaire,[37] and an informant for each participant completed the Informant Questionnaire on Cognitive Decline in the Elderly,[38] in which scores of 70 or lower reflect preserved daily living activities.

Clinical diagnosis of aMCI followed standard guidelines.[39] Scores in one or more cognitive domains, including at least one declarative memory measure, were ≥1.5 SD below the mean for individuals of comparable gender, age, and education level. Also, aMCI patients were not impaired in daily living activities and did not meet clinical criteria for dementia. Exclusion criteria were: 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 high blood pressure, cancer), and chronic use of psychoactive or hypnotic medications. Individuals with medication-controlled hypertension or hypercholesterolemia were included.

Procedure

Sleep/wake cycles were monitored over 14 nights and 15 days in participants' homes with a wrist-worn activity sensor. Participants took memory tests and answered questions about sleep, arousal, and mood each day. Figure 1 shows the experimental design.

On day one, the researcher gave the participant the activity sensor, which was worn continuously throughout the experiment, except during bathing. Participants were also given a sleep log to record bed and wake times that were used in scoring the activity data. The experimenter also administered 2 sleep surveys and 1 memory test. The Pittsburgh Sleep Quality Inventory (PSQI)[40] and the Epworth Sleepiness Scale (ESS),[41] provided information regarding recent sleep habits, quality, and daytime sleepiness. The Warrington Recognition Memory Test (WRMT)[42] included 50 two-alternative-forced-choice recognition trials for words and 50 for faces. The PSQI, ESS, and WRMT were completed only on day 1.

Next, the researcher explained daily tasks and gave the participant a computer and a notebook with daily instructions. Participants practiced daily procedures with the researcher until they could be completed independently. They were asked to complete 3 tasks at a convenient time and at approximately the same time each day. First, participants completed the Karolinska Sleep Diary (KSD)[43] in the notebook to provide subjective sleep assessments from the previous night (Table 2). Also, participants used 5-point scales to rate their current arousal level (1 = very sleepy, 5 = wide awake) and mood (1 = very sad, 5 = very happy). Second, participants took the "24-hour recognition test" in the notebook for items studied the previous day. This test assessed memory when a night of sleep intervened between study and test. Third, participants took the "continuous recognition test" on the computer. This test assessed memory at short retention delays (< 1 min). These 2 tests are described in detail below. The continuous recognition test included items that subsequently appeared on the next day's 24-hour recognition test. Performance on both tests was subject to proactive interference from test items from prior days of the 2-week protocol. However, retroactive interference was minimized in that each day, participants completed the 24-hour recognition test for items studied on the previous day's continuous recognition test before taking a new continuous recognition test.

TABLE 1. Individual aMCI Patient and Group Results for Neuropsychological Testing

Subject	MMSE[32]	CERAD Category Fluency[35]	Boston Naming Test[34]	CERAD Word List Trials 1-3[35]	CERAD Delayed Recall[35]	CERAD Recognition Hits[35]	WMS-R Logical Memory II[36]	CERAD Construc-tions[35]	WRMT Words[42]	WRMT Faces[42]
aMCI 1	28	15	36*	17	5	8*	4*	11	26	36
aMCI 2	26*	13	48	13*	3*	8*	2*	11	36	32
aMCI 3	30	19	55	21	5*	8*	19	7*	43	39
aMCI 4	24*	12	33*	18	4*	10	22	9	44	41
aMCI 5	29	24	58	17*	3*	7*	17	9	42	34
aMCI 6	27*	16	41*	18	5	8*	20	6*	42	31
aMCI 7	30	23	48	20	4*	10	11*	11	47	41
aMCI 8	25*	17	41*	17	4*	10	16*	6*	43	35
aMCI 9	29	14	59	NA	NA	8	7*	11	50	32
aMCI 10	30	30	56	22	4*	10	13*	11	46	21
aMCI group (SE)	27.8 (0.7)	18.3 (1.8)	47.5 (3.0)	18.1 (0.9)	4.1 (0.3)	8.7 (0.4)	13.8 (2.3)	9.2 (0.7)	41.9 (2.1)	37.2 (1.3)
Control group (SE)	29.3 (0.4)	21.7 (1.7)	57.5 (0.7)	25.7 (1.1)	8.9 (0.5)	9.8 (0.1)	22.7 (3.5)	10.2 (0.2)	47.2 (1.4)	42.1 (1.3)

Maximum scores: MMSE = 30, CERAD Category Fluency Test = 99, Boston Naming Test = 60, CERAD Word List Trials 1-3 = 30, CERAD Delayed Recall = 10, CERAD Recognition Hits = 10, WMS-R Logical Memory II = 50, CERAD Constructions Test = 11, WRMT = 50.

*Scores considered impaired on all tests except the WRMT. Normative data for older adults is unavailable for the WRMT.

aMCI indicates amnestic mild cognitive impairment; CERAD, Consortium to Establish a Registry for Alzheimer Disease MMSE, Mini-Mental State Evaluation; WMS-R, Wechsler Memory Scale-Revised; WRMT, Warrington Recognition Memory Test.

Participants phoned the researcher after completing all tasks each day. On day 1, participants did not complete the 24-hour recognition test; on day 15, participants did not complete the continuous recognition test.

For correlational analyses, data were excluded if a participant did not properly complete KSD or memory tests, or when actigraphy measures were ≥ 2 SD from the participant's mean. On average, 1.54 nights were excluded per control and 2.94 per aMCI patient for memory/actigraphy correlations, and 1.96 and 3.36 nights, respectively, for memory/KSD correlations.

Continuous Recognition Test

A sequence of 170 stimuli was centrally presented on the computer screen. Stimuli appeared for 3500 ms coincident with a tone signaling stimulus onset, followed by a blank screen for 500 ms. Using the keyboard, participants were required to press "1" the first time an item appeared and "2" the second time. They were required to respond before the next trial began.

Half of the stimuli were faces (2.75×2.25' color photos from high school yearbooks, gender balanced) and half were words (4 to 10 capitalized letters, 48-point black Helvetica font, matched across days for written frequency and length). Forty faces and 40 words were presented twice during the series. Second presentations occurred at a delay of 4, 16, 32, or 48 s (0, 4, 8, or 12 intervening trials, respectively). Five additional faces and 5 additional words were presented only once.

24-hour Recognition Test

Memory was probed for 12 words and 12 faces learned on the previous day. These 24 items were each presented twice on the previous day's continuous recognition test. Immediately after the continuous recognition test these 24 items were shown again (3500 ms each) as an additional encoding opportunity with instructions that these items should be remembered for a test the next day. This test was given on 2 notebook pages, 1 with 20 words (12 old words randomly intermixed with 8 new words) and the other with 20 faces (12 old faces randomly intermixed with 8 new
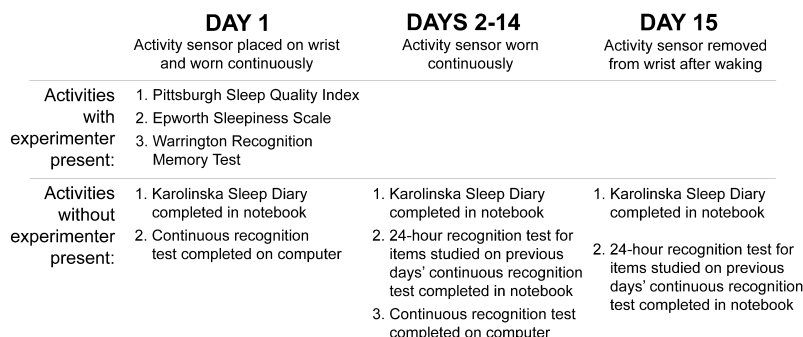
	DAY 1 Activity sensor placed on wrist and worn continuously	DAYS 2-14 Activity sensor worn continuously	DAY 15 Activity sensor removed from wrist after waking
Activities with experimenter present:	1. Pittsburgh Sleep Quality Index 2. Epworth Sleepiness Scale 3. Warrington Recognition Memory Test		
Activities without experimenter present:	1. Karolinska Sleep Diary completed in notebook 2. Continuous recognition test completed on computer	1. Karolinska Sleep Diary completed in notebook 2. 24-hour recognition test for items studied on previous days' continuous recognition test completed in notebook 3. Continuous recognition test completed on computer	1. Karolinska Sleep Diary completed in notebook 2. 24-hour recognition test for items studied on previous days' continuous recognition test completed in notebook

FIGURE 1. Overview of the tasks completed by participants on each of the 15 days of the protocol.

TABLE 2. Actigraphy-derived Sleep Measures and Karolinska Sleep Diary Results, Including Means (With Across-Subject SD in Parentheses) and Mean Intraindividual Variability (IISD)

	Controls		aMCI Patients	
	Mean	**II SD**	**Mean**	**II SD**
Actigraphy parameters				
Bed time	22:52 (0.07)	28 min	23:14 (0.04)	43 min
Wake time (got out of bed)	6:38 (0.05)	40 min	7:16 (0.03)	43 min
Sleep start	23:03 (0.07)	30 min	23:36 (0.04)	50 min*
Sleep end	6:12 (0.05)	43 min	7:00 (0.04)	43 min
Time in bed (min)	466 (61)	42.5	482 (78)	58.9
Total sleep time (min)	375 (52)	42.7	384 (65)	56.4
Wake after sleep onset (min)	54.3 (12)	19.1	60.1 (25)	18.5
Sleep efficiency (%)	80.6 (7.2)	4.9	79.8 (6.8)	6.7
Sleep latency (min)	11.0 (9.2)	10.4	22.2 (19)	23.6
Fragmentation index	37.3 (9.9)	11.6	32.0 (7.8)	9.95
Karolinska Sleep Diary Questions				
What time did you go to bed and turn the light off last night?	22:45 (81)	31.5	23:13 (51)	40.4
What time did you arise this morning?	6:32 (58)	46.8	7:20 (53)	61.5
How long did you sleep? (min)	429 (61)	40	421 (57)	65
How long did it take you to fall asleep? (min)	22.1 (17.4)	11.4	28.1 (18.4)	13.6
How many awakenings did you have last night?	1.8 (0.6)	0.81	1.6 (1.1)	0.60
How many total minutes were you awake after falling asleep last night? (min)	28.2 (17.2)	17.4	32.6 (28.0)	19.4
How did you sleep? (1 = very poorly, 5 = very well)	3.8 (0.7)	0.71	3.8 (0.8)	0.48
Did you feel refreshed after you arose this morning? (1 = not at all, 5 = completely)	4.1 (0.8)	0.53	3.8 (0.06)	0.54
Did you sleep soundly? (1 = very restless, 5 = very soundly)	3.9 (0.7)	0.88	3.8 (0.8)	0.61
Did you sleep throughout the time allotted for sleep? (1 = woke up much too early, 5 = slept thru the night)	3.4 (0.08)	0.81	3.4 (0.8)	0.77
How easy was it for you to wake up? (1 = very easy, 5 = very difficult)	2.3 (1.0)	0.78	2.1 (1.0)	0.50
How easy was for you to fall asleep? (1 = very easy, 5 = very difficult)	2.0 (0.08)	0.92	2.6 (0.9)	0.74
How much did you dream last night? (1 = none, 5 = much)	2.1 (0.9)	0.66	1.9 (1.2)	0.28

*aMCI mean scores significantly different from the control group.

aMCI indicates amnestic mild cognitive impairment; IISD, intraindividual standard deviation.

faces). Participants were instructed to mark the 12 words and 12 faces seen the previous day, marking exactly 12 items per page.

RESULTS

Measures From Day 1

Hit rates from the WRMT were lower in aMCI patients than in controls [79% vs. 89%, respectively; $t(18) = 2.86$, $P < 0.05$, collapsed across words and faces], further documenting the memory abnormality in aMCI. Table 1 shows results separately for words and faces. Self-reports of recent sleep characteristics (PSQI and ESS) were not significantly different between groups.

Daily Memory Measures

24-hour Recognition

Percent correct scores were computed for each participant excluding data from improperly completed tests, yielding a mean of 13.5 tests per control and 11.9 tests per aMCI patient. Percent correct (Fig. 2A) was significantly lower for aMCI patients than for controls [72% vs. 83%, respectively, collapsed across words and faces; $F(1,18) = 12.2$, $P < 0.01$]. The magnitude of this impairment was similar for words and faces.

Continuous Recognition

Results were computed excluding data from improperly completed tests, yielding a mean of 12.3 tests per aMCI patient (one patient's data were excluded entirely) and 13.5 tests per control. Two scores were computed, an immediate memory score (lag 0 intervening trials, hit rate: aMCI = 94%, control = 99%) and a short-delay memory score (collapsing across lags 4, 8, and 12, and corrected by subtracting false-alarm rate from hit rate: aMCI = 53%, control = 80%). Scores were significantly lower for aMCI patients than for controls for both immediate memory [$F(1,17) = 6.81$, $P < 0.05$] and short-delay memory [$F(1,17) = 20.0$, $P < 0.001$]. Figures 2B and C show immediate and short-delay memory scores, respectively, separately for words and faces. Impairments did not differ between words and faces.

Memory Variability

SDs were computed across each participant's daily scores for 24-hour recognition, immediate memory, and short-delay memory (collapsed across words and faces). Intraindividual variability in 24-hour recognition was greater for aMCI patients than for controls [0.08 and 0.06, respectively; $t(18) = 3.19$, $P < 0.01$]. Patients were also more variable than controls for immediate memory [aMCI = 0.07, control = 0.03; $t(17) = 2.74$, $P < 0.05$] and short-delay memory [aMCI = 0.11, control = 0.07; $t(17) = 2.99$, $P < 0.01$].
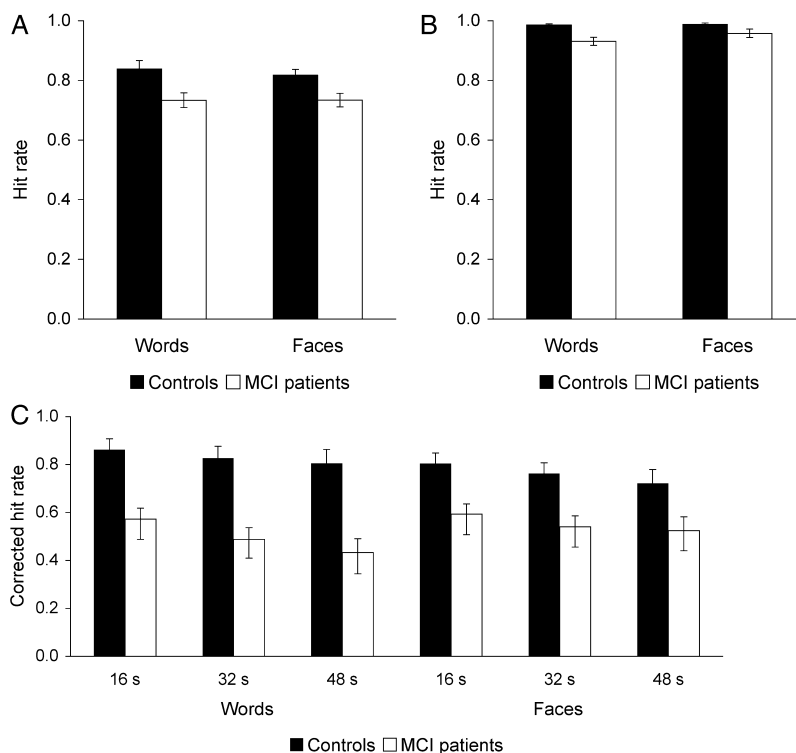
FIGURE 2. Recognition hit rates for amnestic mild cognitive impairment (aMCI) Patients and controls averaged across 14 nights for each participant and then averaged across all participants for (A) 24-hour recognition, (B) immediate memory (from the continuous recognition test, lag=0 intervening trials), and (C) short-delay memory as a function of retention delay in the continuous recognition test, corrected for false alarms. Bars represent SEs of the mean.

Daily Sleep Measures

Actigraphy parameters (selected a priori based on results in AD[20]) failed to reveal significant differences between groups. Results from KSD questions also revealed no group differences (Table 2). An analysis of across-night SD for each individual for each actigraphy measure and KSD question revealed that aMCI patients were more variable than controls on the actigraphy sleep-start measure only [$t(18) = 2.47$, $P < 0.05$].

Relationships Between Daily Sleep and Daily Memory

For each participant, daily 24-hour recognition percent correct scores were regressed with each of the daily sleep measures concerning the intervening night, and Pearson correlation coefficients were calculated. Table 3 lists the average r values for these correlations for each group. Each individual's r value was transformed to Fisher's Z, and paired t tests were performed on the Z-transformed coefficients for each comparison for each group to determine if correlations significantly differed from zero (no relationship). All correlations were nonsignificant in controls.

Coefficients for aMCI patients were positive and significantly greater than zero for the correlation between the 24-hour recognition and the time-in-bed actigraphy measure [$t(9) = 2.86$, $P < 0.05$]. Recognition was better when time in bed was longer. A relationship with fragmentation index was also apparent [$t(9) = 2.30$,

$P < 0.05$], but we are cautious about this result because coefficients were strongly positive in 3 subjects and negative in 4 others.

Relationships were found between 4 KSD questions and 24-hour recognition in aMCI patients. Recognition correlated positively with questions regarding whether participants slept through the time allotted for sleep [$t(9) = 3.39$, $P < 0.05$], how well participants slept [$t(9) = 2.63$, $P < 0.05$], and the time participants arose each morning [$t(9) = 3.81$, $P < 0.005$]. In these comparisons, ratings indicative of better sleep predicted better memory. A negative relationship was found with how easy it was to fall asleep [$t(9) = 2.31$, $P < 0.05$]. As difficulty in falling asleep increased, memory decreased.

Because nonsignificant relationships in controls could merely reflect limited variability, a permutation analysis was conducted for each of the significant relationships observed in aMCI patients. For each relationship, 1000 random permutations were generated, each reflecting one realization of the mean difference of the correlation coefficients between the groups.[44] The permutations generated a distribution of these mean differences, which was used to calculate a 2-tailed P value for the observed difference in mean coefficients between aMCI patients and controls. The differences in coefficients for the KSD measures of sleeping through the time allotted for sleep and how easy it was to fall asleep were significant ($P < 0.005$ and $P < 0.05$, respectively), indicating that these relationships were more strongly positive in aMCI patients than in

TABLE 3. Average Pearson Correlation Coefficients for Intraindividual Correlations Between 24-hour Recognition Percent Correct Scores and (1) Actigraphy Parameters and (2) Responses to Karolinska Sleep Diary questions, for Controls and aMCI Patients

	Controls	aMCI Patients
Actigraphy parameters		
Bed time	0.10	− 0.14
Wake time	− 0.03	0.09
Sleep Start	0.12	0.02
Sleep End	− 0.06	0.16
Time in bed	− 0.07	0.20*
Total sleep time	− 0.03	0.10
Wake after sleep onset	− 0.12	0.07
Sleep efficiency	0.15	0.01
Sleep latency	− 0.04	0.18
Fragmentation index	0.01	0.31*
Karolinska Sleep Diary Questions:		
What time did you go to bed and turn the light off last night?	0.18	− 0.08
What time did you arise this morning?	0.05	0.23*
How long did you sleep?	0.01	0.08
How long did it take you to fall asleep?	− 0.03	− 0.16
How many awakenings did you have last night?	− 0.05	− 0.07
How many minutes were you awake after falling asleep last night?	− 0.15	0.05
How did you sleep?	− 0.03	0.29*
Did you feel refreshed after you arose this morning?	0.06	0.14
Did you sleep soundly?	− 0.10	0.12
Did you sleep throughout the time allotted for sleep?	− 0.04	0.44*
How easy was it for you to wake up?	0.05	− 0.01
How easy was it for you to fall asleep?	0.05	− 0.13*
How much did you dream last night?	− 0.06	0.52

*Correlation coefficients that were significantly different from zero.
aMCI indicates amnestic mild cognitive impairment.

controls. Coefficient differences were not significant between the groups for the other relationships between 24-hour recognition and sleep found in aMCI.

Relationships Between Subjective and Objective Measures of Sleep

Some KSD questions overlapped with information in the actigraphy measures. The bed time and wake time actigraphy measures were derived from the sleep log associated with the activity sensor, so these numbers should be identical to the first 2 KSD questions. Yet, means differed slightly (Table 2), likely reflecting the fact that sleep logs were completed immediately before and after sleep, whereas KSD questions were completed coincident with the daily memory tests. Nonetheless, these measures were highly correlated in aMCI patients [bed time: $t(9) = 3.02$, $P < 0.05$; wake time: $t(9) = 4.60$, $P < 0.005$] and controls [bedtime: $t(9) = 3.60$, $P < 0.01$; wake time: $t(9) = 3.93$, $P < 0.005$]. Actigraphy-measured total sleep time also correlated with KSD responses regarding how long participants slept [aMCI: $t(9) = 3.64$, $P < 0.01$; control: $t(9) = 6.48$, $P < 0.001$]. Both groups were worse at estimating how long it took to fall asleep and how long they were awake after falling asleep, as these KSD responses were not significantly correlated with corresponding actigraphy measures (sleep latency and wake after sleep onset, respectively).

To delineate relationships between the KSD questions associated with 24-hour recognition in aMCI patients and actigraphy, these KSD responses were regressed with each of the actigraphy parameters obtained for the corresponding night for each aMCI patient. For each comparison, individual r values were transformed to Fisher's Z, and paired t tests were performed to assess significance. The question regarding what time participants arose each morning was positively correlated with actigraphy measures for wake time [$t(9) = 4.85$, $P < 0.001$], sleep end [$t(9) = 5.84$, $P < 0.001$], time in bed [$t(9) = 4.02$, $P < 0.01$], and total sleep time [$t(9) = 3.76$, $P < 0.01$]. The question regarding whether participants slept throughout the time allotted for sleep was positively correlated with wake time [$t(9) = 2.48$, $P < 0.05$] and sleep start [$t(9) = 2.46$, $P < 0.05$], and the question asking how well participants slept was positively correlated with wake time [$t(9) = 4.75$, $P < 0.01$] and sleep end [$t(9) = 2.96$, $P < 0.05$]. The question about how easy it was to fall asleep was not related to any actigraphy parameters. These results indicate that subjective sleep assessments are not orthogonal to actigraphy.

Relationships Between Sleep Variability and Memory

To determine if across-day sleep variability predicted memory impairment, for each sleep parameter, the across-day SD for each participant was correlated with the average 24-hour recognition score for each participant. Correlations were also computed between sleep variability and a declarative memory measure from the neuropsychological battery, the Logical Memory II subtest of the WMS-R.[36] To maximize power, correlations were performed for aMCI patients and controls together (one control did not complete the WMS-R). Variability did not predict average 24-hour recognition, but variability in 4 actigraphy measures predicted Logical Memory II: time in bed ($r = − 0.484$, $P < 0.05$), total sleep time ($r = − 0.533$,
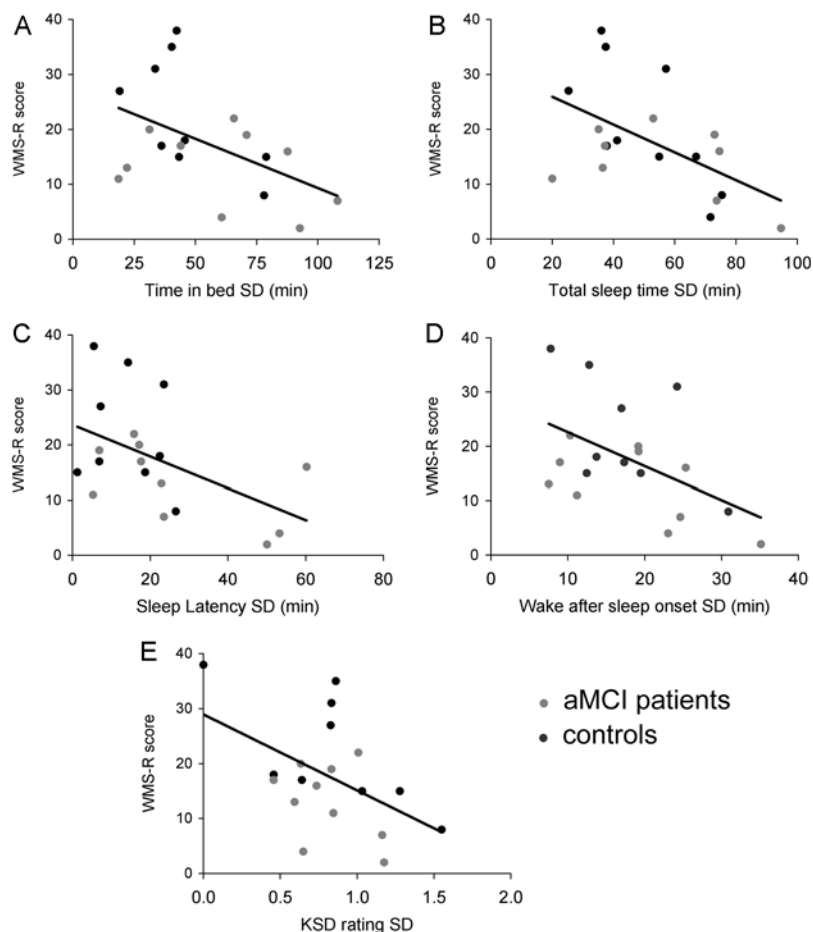
FIGURE 3. SD of the (A) time in bed, (B) actual sleep time, (C) sleep latency, (D) wake after sleep onset actigraphy measures, and (E) ratings given to the Karolinska Sleep Diary (KSD) question regarding how well participants slept throughout the time allotted for sleep across the 14 nights of the protocol, plotted against the Logical Memory II delayed recall score from the Wechsler Memory Scale-Revised (WMS-R). aMCI indicates amnestic mild cognitive impairment.

$P < 0.05$), sleep latency ($r = -0.492$, $P < 0.05$), and wake after sleep onset ($r = -0.498$, $P < 0.05$). Participants with relatively higher variance showed relatively poorer memory. Higher variability in KSD ratings to the question regarding whether participants slept through the time allotted for sleep was also associated with lower recall ($r = -0.478$, $P < 0.05$). Actigraphy and KSD measures correlated with WMS-R recall are depicted in Figure 3.

Relationships Between Sleep and Other Factors

Various processes that contribute to successful memory might be impaired as an indirect result of poor sleep, independent of memory processing during sleep. For example, drowsiness could reduce the ability to encode or retrieve information, as drowsy individuals might experience more difficulty paying attention to the task. If so, the sleep parameters that showed relationships with 24-hour recognition might show relationships with immediate or short-delay memory measures. However, this was not the case. Also, no sleep measures showed relationships with daily mood or arousal ratings. Although participants were allowed to choose the time of day they would complete the daily tasks, the time between waking up and daily testing was not significantly different between groups [$t(18) = 0.15$,

and this time interval was not correlated with mean 24-hour recognition scores ($r = -0.03$).

DISCUSSION

This experiment revealed a novel sleep-memory connection; daily variations in subjective sleep quality in aMCI patients predicted daily variations in memory for information learned the previous day. Thus, it seems that poor memory in aMCI patients is due in part to disrupted memory consolidation during sleep. A general memory or cognitive disruption independent of a consolidation explanation is unlikely, as sleep measures related to 24-hour recognition were not correlated with immediate or short-delay memory, nor was daily memory mediated by mood, arousal level, or the time elapsed between waking and when the tests were taken.

In aMCI patients, subjective assessments of how well an individual slept, whether they slept throughout the time allotted for sleep, how easy it was to fall asleep, the time an individual arose, and the time-in-bed actigraphy measure were related to 24-hour recognition, whereas no relationships were observed in controls. The presence of significant relationships in aMCI patients but not in controls could indicate that sleep-dependent consolidation is abnormal in

aMCI, and this notion is supported by further analyses revealing that the strength of some relationships were reliably different between groups. Alternatively, the lack of sleep-memory relationships in controls could reflect the much smaller across-day memory variance in controls. Our recognition tests facilitated data acquisition, and were designed so that aMCI patients could complete them independently with above-chance accuracy. More difficult memory tests (eg, recall) may be necessary to reveal sleep-memory relationships in healthy older adults. Nonetheless, the significant relationships in aMCI patients indicate that poor sleep is contributing to poor memory consolidation in these individuals.

Declarative memory was studied here, as memory deficits are typically restricted to declarative tasks in aMCI.[45] Our aMCI patients exhibited declarative memory impairments in the form of reduced accuracy and increased intraindividual variability, both of which have been demonstrated previously in AD[46] and aMCI.[47] Yet, sleep also benefits nondeclarative memory consolidation.[48] Determining which sleep parameters uniquely impact declarative memory will be important for specifying how aMCI pathology affects sleep-dependent consolidation.

Subjective sleep assessments also correlated with some actigraphy parameters. As the time when patients woke up increased, responses to 3 KSD questions became more positive, suggesting that sleeping later positively impacts perceived sleep quality. According to Kahneman and Riis's[49] "remembering self" concept, retrospective evaluations of an episode are thought to rely more strongly on the conclusion of the episode. Therefore, positive feelings typically associated with sleeping late could play a prominent role in subjective sleep assessments for such a night. Subjective assessments could also reflect particular sleep stages or other physiological sleep characteristics not captured by actigraphy, and/or other internal factors associated with cognitive decline. At present, it is unclear how each of these factors contributes to KSD measures. Evaluations of subjective and objective sleep-measure concordance indicate frequent discrepancies, especially in patient populations.[50,51] Subjective assessments may reflect sleep continuity and SWS amount,[52] or a more complex combination of objective parameters.[53] Ultimately, deciphering how subjective assessments relate to objective sleep indices and other factors will aid in understanding sleep-dependent consolidation in aMCI.

The dramatic sleep disruptions common in AD were not found in aMCI, as aMCI patients did not exhibit abnormalities in actigraphy, KSD responses, recent sleep habits, sleep quality, or daytime sleepiness. Actigraphy measures reported here were comparable to previous results in healthy older adults,[54] indicating that idiosyncrasies in our controls do not underlie the lack of group differences in the actigraphy measures. As aMCI often portends AD, large sleep disturbances may not appear until clinical AD emerges. More subtle sleep changes in aMCI may exist such as changes in sleep-cycle duration, time spent in each sleep stage, and electroencephalogram spectral power. We are therefore exploring this possibility using PSG measures in ongoing studies of aMCI.

Despite the lack of significant between-group differences in sleep, our data hints that sleep is not normal in aMCI. For instance, we observed trends for later sleep start and end times and longer sleep latencies in aMCI patients (Table 2). These trends are consistent with phase-delayed circadian rhythms observed in AD patients,[55] suggesting a possible phase-delay in aMCI. Increased intraindividual variance was also apparent in several actigraphy measures in the aMCI group, although only sleep-start variance was significantly larger than in controls. Future studies using larger sample sizes may confirm that these trends reflect sleep disruptions in aMCI.

Intraindividual sleep variability was also linked with memory in our study. Participants who exhibited greater across-night sleep variability showed lower story-recall during the neuropsychological battery administered before the sleep protocol. Thus, inconsistent sleep was associated with poor recall. Sleep variability did not correlate with recognition from our daily memory tests, perhaps because recognition is not as sensitive as recall to neural dysfunction associated with erratic sleep across nights. A likely assumption is that participants who exhibited inconsistent sleep during our protocol also did so prior to neuropsychological testing. Whereas a night of sleep may be important for consolidating information learned the previous day, inconsistent sleep across nights may impair neural systems required for good recall. These findings suggest that sleep may influence memory in multiple ways.

Although large sleep abnormalities were not found in aMCI, the present results indicate that aMCI patients undergo changes that influence both their subjective sleep quality and overnight memory processing. Neuropathology in aMCI and AD typically includes damage to memory networks[24,25] and also to sleep regulation regions; the locus coeruleus and nucleus basalis.[56] Disruptions in sleep-dependent memory consolidation may manifest in multiple ways. Our methods were advantageous because they provided sleep data in home environments for an extended period. Yet, a recent report described physiologic alterations in post-learning sleep in AD.[57] Thus, PSG is needed to determine more thoroughly how aMCI pathology may affect sleep-dependent consolidation. The present results highlight the need for further analysis of relationships between disrupted memory and sleep.

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