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Original Article

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Rapid eye movement sleep mediates age-related decline in prospective memory consolidation

Michael K. Scullin[1,*], Chenlu Gao[1], Paul Fillmore[2], R. Lynae Roberts[1], Natalya Pruett[1], and Donald L. Bliwise[3]

[1]Department of Psychology and Neuroscience, Baylor University, Waco, TX, [2]Department of Communication Sciences and Disorders, Baylor University, Waco, TX, and [3]Department of Neurology, Emory University School of Medicine, Atlanta, GA

*Corresponding author. Michael Scullin, Baylor University, One Bear Place 97334, Waco, TX 76798. Email: michael_scullin@baylor.edu.

Abstract

Study Objectives: Prospective memory, or remembering to execute future intentions, accounts for half of everyday forgetting in older adults. Sleep intervals benefit prospective memory consolidation in young adults, but it is unknown whether age-related changes in slow wave activity, sleep spindles, and/or rapid eye movement (REM) sleep mediate hypothesized effects of aging on prospective memory consolidation.

Methods: After an adaptation night, 76 adults aged 18–84 completed two experimental nights of in-laboratory polysomnography recording. In the evening, participants encoded and practiced a prospective memory task and were tested the next morning. On a counterbalanced night, they encoded and practiced a control task, and were tested the following morning.

Results: Increasing age predicted worse prospective memory consolidation ($r = -.34$), even when controlling for encoding, speed, and control-task performance (all $ps < .05$). Frontal delta power, slow oscillations, and spindle density were not related to prospective memory consolidation. REM sleep duration, however, explained significant variance in prospective memory consolidation when controlling for age ($\Delta R^2 = .10$). Bootstrapping mediation showed that less REM sleep significantly mediated the aging effect on prospective memory consolidation [$b = -.0016$, $SE = 0.0009$ (95% confidence interval [CI] = −0.0042 to −0.0004)]. REM sleep continued to mediate 24.29% of the total effect of age on prospective memory after controlling for numerous demographic, cognitive, mental health, and sleep variables.

Conclusion: Age-related variance in REM sleep is informative to how prospective memory consolidation changes with increasing age. Future work should consider how both REM sleep and slow wave activity contribute, perhaps in a sequential or dynamic manner, to preserving cognitive functioning with increasing age.

Statement of Significance

Whether one needs to remember to take a new medication, deliver a message to a colleague, or pick up milk at the grocery store, the ability to remember to execute delayed intentions is essential to independent living. Because intentions typically cannot immediately be performed, they must undergo memory consolidation. The current study identified an age-related deterioration in the consolidation of delayed intentions. Furthermore, this deterioration might be attributed to reduced REM sleep duration with increasing age. Behavioral and pharmacological interventions that target REM sleep will be critical to establish causality and translation to clinical settings.

Key words: intention; prospection; older adults; polysomnography; slow wave activity; sleep spindles; rapid eye movement sleep; spontaneous retrieval; preplay

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Introduction

For 2,000 years, scholars conceptualized memory as functioning to record the past (Plato's *Theaetetus*) [1]. Today, however, cognitive neuroscience conceptualizes memory as functioning to prepare us for the future [2]. This future-oriented, "preplay" [3] model of memory is well-captured by the study of *prospective memory*, that is, the ability to remember to perform delayed intentions. Prospective memory failures account for half of everyday forgetting errors [4] and have been linked to catastrophes such as airplane crashes [5], retained surgical instruments [6], and forgetting that a sleeping child is in the backseat of one's car [7]. Less dramatic, but more ubiquitous, is the use of prospective memory to return messages, pick up medications from the pharmacy, and take a different route to work that avoids construction [8].

Sleep and prospective memory

Sleep deprivation impairs prospective memory [9–12] whereas normal sleep facilitates prospective memory consolidation [13–18]. However, there exists minimal data on which component of sleep physiology—slow-wave activity (SWA), sleep spindles, or rapid eye movement (REM) sleep—facilitate prospective memory consolidation [15]. To inform predictions for how sleep consolidates prospective memories, it is important to first consider how tests of prospective memory are different from traditional tests of motor/procedural memory and episodic/declarative memory. In the latter tests, participants are placed into an effortful retrieval mode during testing [19], such that the experimenter tells participants to try to perform a motor sequence or to recognize studied words. In prospective memory tests, no reminders are given, and thus, participants must "remember to remember." [7] The ability to "remember to remember" depends on the associative strength between *what* must be remembered (intention) and *when* it must be remembered (cue) [20]. When the cue-intention association is strong (e.g. due to being consolidated during sleep), then processing the retrieval cue will spontaneously/automatically trigger retrieval of the intention [21, 22].

SWA and spindles are typically implicated in supporting episodic memory consolidation, whereas REM sleep is classically implicated in supporting procedural memory consolidation [23]. However, the collective literature indicates that dichotomizing the function of sleep stages by procedural vs. episodic memory *systems* is less informative than identifying how macro- and micro-features of sleep interact in response to specific memory *processes* [24]. As one example, while SWA promotes retention of neutral information, REM sleep can enhance emotional processing and binding of future-relevant associations [23–26].

Llewellyn and Hobson's theoretical model [27] seems particularly relevant to the current work on prospective memory. They proposed that REM sleep evolved to help prepare organisms for future automatic actions. In Llewellyn and Hobson's words, REM sleep functions "to enable effective preplay, [that is, the future stimulus] can be acted upon unconsciously and rapidly" (p. 81) [27]. Following their conceptualization, because prospective memory is a future-oriented behavior depending on spontaneous/automatic associative processes [28, 29], REM sleep activity may facilitate prospective memory consolidation.

Sleep, aging, and memory consolidation

A broader goal for the sleep and memory consolidation field is to inform cognitive aging [30–33]. A meta-analysis on sleep, aging, and memory consolidation, however, found substantial variability across aging studies in memory-polysomnography correlations and memory outcomes (i.e. age preservation vs. impairment of memory consolidation) [34]. The inconsistencies might reflect small samples, multiple comparisons, and that most studies have not disentangled consolidation deficits from known age-related deficits in processing speed and effortful retrieval [35]. Testing prospective memory provides a potential solution to these processing speed and retrieval challenges. Specifically, in laboratory settings, prospective memory is tested against the background of a speeded ongoing decision-making task to mirror the real-world scenario of having to remember an intention (such as stopping at the grocery store), while performing ongoing activities (such as driving one's car). Measuring ongoing task performance at the same time as memory is being tested allows for the control of processing speed. In addition to controlling processing speed, tests of "focal" event-based prospective memory (i.e. tests with strong environmental cues) have found that spontaneous/automatic *retrieval* processes are generally preserved in advancing age [36, 37] (by contrast, tests of "nonfocal" prospective memory that depend on sustained, vigilant monitoring consistently show age-related declines [28]). Utilizing a focal prospective memory test that shows age-preservation of retrieval processes, and statistically controlling for ongoing task performance, provides a closer look at whether aging specifically compromises memory consolidation.

If aging does compromise memory consolidation, then changes in NREM or REM activity might mediate these effects. Some studies found SWA and/or spindle density to mediate age-related memory decline [38, 39], and three experiments that boosted SWA and/or spindles in older adults also improved episodic memory [40–42]. Though NREM processes are certainly important to memory functioning [43], over the past 50 years, greater REM sleep has been a more consistent cross-sectional and longitudinal predictor of cognitive longevity [44–46]. The historical evidence linking REM sleep to better cognitive aging [47], when coupled with theorizing that REM preplays future-relevant associations [27], leads to the prediction that aging will compromise prospective memory to the extent that REM sleep declines.

Methods

Overview of design

Adult participants were recruited for a three-night study. Baseline night data have previously been reported [48]. On night 2 and night 3, participants encoded a prospective memory task and a control task, respectively (night order counterbalanced). In the morning, we tested task performance and evaluated: (1) whether prospective memory task performance declined with increasing age, (2) whether SWA, spindle density, or REM sleep during the preceding night mediated age differences in prospective memory performance, and (3) whether these results were robust when controlling for encoding, control-task, and ongoing task performance.

Participants

Eighty healthy adults between the ages of 18 and 84 completed the prospective memory and polysomnography procedures. Participants were recruited through fliers, local news advertisements, and outreach programs in the central Texas area. Exclusion criteria included taking prescribed medications that were known to affect sleep (selective serotonin reuptake inhibitors, sedative-hypnotics, cholinesterase inhibitors); having a history of psychiatric or neurological disorders; or having a history of insomnia, narcolepsy, or an apnea–hypopnea index (AHI) ≥30 during the adaptation night. All participants scored 24 or higher on the Mini-Mental State Examination (MMSE), which is a common cutoff for dementia screening [49]. For generalizability, we did not exclude participants with mild-to-moderate sleep apnea. We excluded two participants for not completing all three study nights, one participant due to a protocol deviation (repeated conditions), and one participant for not returning for night 3 until after longer than 1 month (mean number of days between night 2 and night 3 was 1.63 ± 1.36 days). Descriptive data for the remaining 76 participants are presented in Table 1. The study was approved by the Baylor Institutional Review Board and all participants provided informed consent.

Sleep measurement

Overnight polysomnography was recorded in a sound-attenuated sleep laboratory using Grass Comet XL Plus systems. The polysomnography montage consisted of electroencephalography (EEG) from Fp1, Fp2, F3, F4, Fz, C3, C4, P3, P4, Pz, O1, O2, and Oz (grounded at Fpz and Cz locations, referenced to contralateral mastoids), recorded at 200 samples per second. The montage further included left and right electrooculography (EOG), mentalis electromyography (EMG), and breathing measures (nasal pressure, chest and abdomen movements, finger pulse oximetry). Sleep stages were scored in 30-s epochs by a certified polysomnography technician according to AASM guidelines [50], and masked to condition. PSG variables included total sleep time, sleep efficiency, sleep onset latency, wake after sleep onset, AHI, and sleep stages (N1, N2, N3, and REM sleep).

SWA spectral power analysis

Spectral analysis of SWA is considered to be a better measure of slow wave quality than duration of visually scored slow-wave sleep (SWS/N3) [31]. We used Brain Products BrainVision Analyzer 2.0 software to conduct such analyses. Visual inspection for confounding effects of movement or electrode artifact was performed by trained research personnel, and epochs containing artifact (on average 1.82% of all epochs) were excluded from all analyses. The EEG data were band-pass filtered with high- and low-pass cutoffs of 0.3 and 35 Hz and sampling rate was modified to 128 Hz. Each participant file was segmented into equal 4-s segments, and we applied symmetric Hanning window with 50% overlap to decrease edge effects. We excluded EEG data during wake epochs. Using the remaining sleep epochs, we performed fast Fourier transform (FFT) with a resolution of 0.25 Hz to generate spectral power density ($\mu V^2/Hz$) at all scalp channels for each of the following frequency bands: 0.5–1 Hz (slow oscillations), 1–4 Hz (delta SWA), 4–8 Hz (theta), 8–12 Hz (alpha), 12–16 Hz (sigma), and 16–32 Hz (beta). We analyzed slow oscillations and delta SWA using three approaches: (1) averaged across all electrodes and the entire night, (2) averaged across only frontal electrodes during NREM, and (3) averaged across only frontal electrodes during SWS.

Spindle detection analysis

There are several procedures for counting sleep spindles, but not all methods are equally valid. When comparing six automated spindle analysis methods to expert consensus labeling [51], Wamsley and colleagues' wavelet-based algorithm [52] produced the best agreement of the automated detectors. In

Table 1. Demographic, neuropsychological testing, sleep/circadian questionnaire, and health information

	Adults < 30 years (n = 40)	Adults ≥ 30 years (n = 36)	Overall sample (N = 76)	Correlation with chronological age
Age (in years)	20.28 ± 1.68	62.08 ± 12.83	40.08 ± 22.80	—
Gender (% female)	60.0%	50.0%	55.3%	$r(74) = .16, p = .16$
Race/ethnicity (% Caucasian)	57.5%	75.0%	65.8%	$r(74) = .27, p = .02$
Education (in years)	14.11 ± 1.16	15.70 ± 3.97	14.85 ± 2.93	$r(73) = .21, p = .07$
MMSE (of 30)	28.78 ± 1.19	28.03 ± 1.63	28.42 ± 1.45	$r(74) = -.21, p = .07$
Working memory reading span (of 30)	23.44 ± 4.35	17.32 ± 6.91	20.54 ± 6.45	$r(74) = -.51, p < .001$
Phonemic fluency (summed FAS)	39.20 ± 8.85	34.69 ± 10.54	37.07 ± 9.89	$r(74) = -.24, p = .04$
Semantic fluency (summed categories)	47.73 ± 9.84	41.17 ± 9.96	44.62 ± 10.37	$r(74) = -.32, p = .01$
Mill Hill Vocabulary (proportion correct)	0.70 ± 0.12	0.65 ± 0.13	0.68 ± 0.13	$r(74) = -.16, p = .16$
PRMQ—total (of 80)	40.05 ± 5.79	37.15 ± 10.25	38.72 ± 8.22	$r(72) = -.27, p = .02$
PSQI—global score	4.70 ± 2.19	6.19 ± 3.54	5.41 ± 2.99	$r(74) = .22, p = .06$
PSQI—habitual bedtime	00:18 ± 72.29 min	22:28 ± 68.84 min	23:25 ± 89.32 min	$r(74) = -.62, p < .001$
PSQI—habitual wake time	08:10 ± 75.46 min	06:45 ± 76.82 min	07:30 ± 86.77 min	$r(74) = -.48, p < .001$
ESS—total score	8.87 ± 3.31	8.19 ± 4.41	8.54 ± 3.87	$r(72) = -.14, p = .24$
MEQ—total score	65.83 ± 9.75	57.81 ± 9.69	62.03 ± 10.46	$r(74) = -.26, p = .02$
GDS—total score	2.25 ± 2.23	2.67 ± 2.95	2.45 ± 2.58	$r(74) = -.09, p = .43$

Inferential statistics were conducted using chronological age as a continuous variable, though we also provide descriptive data separated at age 30 for illustrative purposes. There were missing data for years of education (n = 1), PRMQ (n = 2), and ESS (n = 2).

ESS = Epworth Sleepiness Scale; GDS = Geriatric Depression Scale; MEQ = Morningness-Eveningness Questionnaire; MMSE = Mini-Mental Status Examination; PSQI = Pittsburgh Sleep Quality Index; PRMQ = Prospective Retrospective Memory Questionnaire.

brief, Wamsley's algorithm uses Morlet wavelet to perform time-frequency transformation on raw EEG data. Then, the algorithm automatically detects EEG events in the 10–16 Hz frequency range and identifies events exceeding 4.5 times the mean signal amplitude of artifact-free epochs that have a minimum duration of 300 ms [51]. We implemented Wamsley's method in Matlab 9.0 during artifact-free epochs averaged across frontal channels (resampled to 100 Hz) to quantify N2 and SWS spindle density.

Questionnaire and neuropsychological measures

Each night, participants were asked to complete questionnaires during electrode application to keep them awake and engaged. The questionnaires that were relevant to sleep and prospective memory are displayed in Table 1 (additional detailed analyses in Supplementary Table S1), and include the Pittsburgh Sleep Quality Index (PSQI) [53], Epworth Sleepiness Scale (ESS) [54], Morningness-Eveningness Questionnaire [55], Geriatric Depression Scale [56], and Prospective and Retrospective Memory Questionnaire (PRMQ) [57]. We also assessed semantic memory (three vocabulary tests), working memory capacity (automated reading span) [58], semantic fluency (categories of animals, fruits, and cars) [59], and phonemic fluency (FAS—Controlled Oral Word Association Test) [60]. Participants were also asked to maintain a sleep diary before laboratory sessions to track recent sleep durations and napping.

Procedure

Participants arrived before 21:00 h and they completed questionnaires, electrode application, and 20 min of assorted cognitive tasks. After those tasks, participants were randomly assigned to the prospective memory task procedures or the control task procedures (within-subjects design with night order counterbalanced). We used a prospective memory task that typically shows age-preservation of retrieval processes [36, 37] and has previously been used to show sleep-dependent memory consolidation effects in young adults [13].

As illustrated in Figure 1, in laboratory-based tests of prospective memory, participants are first introduced to background, "ongoing" tasks before being given their prospective memory intention [61]. One ongoing task was *category decision*, in which participants responded yes or no whether two words belonged to the same category (by pressing keys labeled on the number pad). A second ongoing task was *lexical decision*, in which participants responded yes or no whether a series of letters formed a word or nonword. A third ongoing task was *living/nonliving decision* in which participants responded yes or no whether a noun represented a living object. Participants completed evening warm-up baseline blocks of each task. The ongoing task order was randomized for each participant.

Following the evening warm-up baseline blocks, participants were told, via computer instructions, that there was an interest in their ability to remember to perform an action in the future (i.e. prospective memory). In addition to the computerized tasks they would perform the next morning, if they ever saw the words "table" or "horse" then they should remember to press the P key on the keyboard. Following the recommended approach in prospective memory studies [62], participants were told that they could press the P key immediately or on the following few trials, and that no one would remind them to perform this task. To ensure that all participants encoded the prospective memory instructions, they were required to repeat them out loud three times with the experimenter present. They then completed a practice block of pressing the P key in response to a target word.

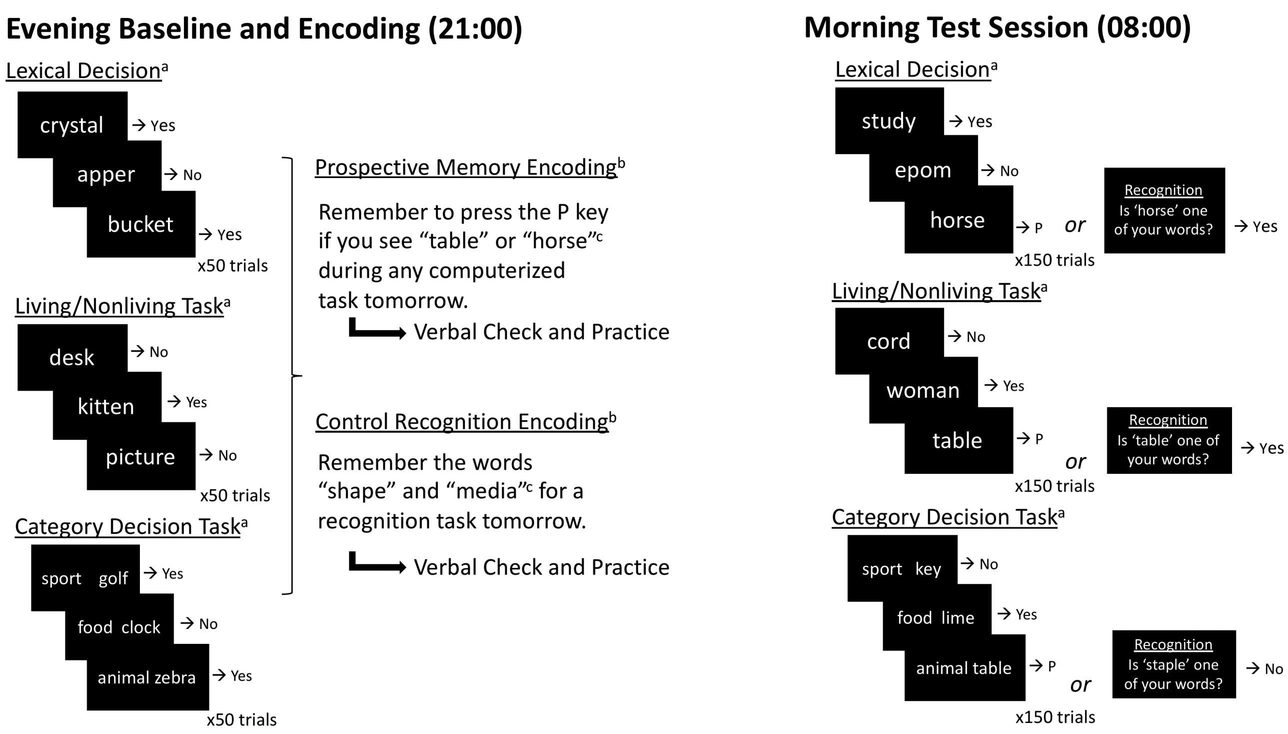

Figure 1. Prospective memory testing procedure. Participants completed three ongoing tasks with a prospective memory or control recognition task embedded. [a]Ongoing task order was randomized. [b]Prospective memory and control task order were counterbalanced. [c]Target word set was counterbalanced across conditions.

During the counterbalanced control night, the procedures were identical with two exceptions. First, participants were given the control task of retaining the control words "shape" and "media" for experimenter-prompted recognition tests the following day. Second, the ongoing task stimuli lists, as well as the shape/media and horse/table word sets, were counterbalanced across conditions.

By comparing ongoing task performance across the counterbalanced prospective memory and control task days, one can model the extent to which having a prospective memory task interferes with ongoing task performance. If ongoing task performance consistently suffers on the prospective memory day relative to the control day, then that indicates that participants were vigilantly monitoring (searching) for prospective memory cue words [63]. If performance does not suffer before prospective memory cues, then retrieval is dependent on spontaneous/automatic processes. The efficacy of spontaneous/automatic retrieval processes is known to depend on the strength of the cue-intention association (for detailed theoretical overview, see the Multiprocess Framework of Prospective Memory [7, 20]). Recent work shows that participants will transiently monitor during test sessions, but that during periods in which monitoring is disengaged, participants can still spontaneously retrieve an intention if the cue-intention link is strong (e.g. consolidated) [8, 20]. Previous work on sleep and prospective memory consolidation in young adults indicates that sleep consolidates the cue-intention association, rather than increases vigilant monitoring [13, 14].

Lights out was at approximately 22:30, and next-day lights on was at 07:30. Thus, time in bed was 9 h. In the morning, after being allowed to use the restroom, drink water, and get dressed, participants completed several test blocks (Figure 1). Participants were not reminded of the prospective memory or control tasks. Across the three ongoing task test blocks, there were a total of 450 trials (a 500 ms blank screen occurred between trials). Responding with the yes, no, or P keys advanced the screen to the next trial. Twelve prospective memory trials were interspersed across the three test blocks (in the control condition, there were 12 interspersed recognition tests). It is critical that the prospective memory cue words occur rarely, otherwise participants will continuously monitor, thereby changing the nature of the task from testing spontaneous/automatic prospective memory processes to simply testing vigilance and cue rehearsal [62].

Statistical analyses

First, we used analysis of variance/covariance (ANOVA/ANCOVA) and Pearson product-moment correlations to investigate whether prospective memory performance declined in relation to ongoing task context and chronological age. Chronological age was treated as a continuous variable in all inferential statistical analyses, though in some tables and figures we also reported descriptive data separated by age 30 (e.g. most memory consolidation studies only enroll young adults under the age of 30). Prospective memory consolidation was expressed as morning performance after regressing evening practice performance (standardized residual scores), to protect against the statistical limitations of difference scores (note, however, that the primary findings all replicated when solely using morning performance) [64]. Second, we examined correlations between prospective memory consolidation and hypothesized polysomnography variables (SWA, spindle density, REM), controlling for chronological age, and correcting for multiple comparisons. Third, to test sleep as a mediating variable of age effects on prospective memory consolidation, we conducted a bootstrapping mediation analysis. We conducted the mediation analysis first without adjustment, second after adjusting for performance on the control and ongoing tasks, and third after adjusting for a broader range of variables that have previously been implicated in sleep and aging relationships [65], including demographic, cognitive, and mental health factors (Table 1). Statistical analyses were implemented in SPSS version 23.

Results

Sleep across prospective memory and control nights

Table 2 demonstrates that most sleep variables demonstrated strong inter-night correlations. No polysomnography variable differed significantly across prospective memory and control-task nights (note that data were missing for two control nights). However, as expected, there were widespread age-related changes in polysomnography variables. With increasing age, there was greater sleep fragmentation (sleep efficiency, wake after sleep onset) and higher AHIs. Older participants showed longer N1 sleep, but shorter SWS and REM sleep. Aging severely disrupted SWA and N2 frontal spindle density (Table 3).

Table 2. Sleep stage scoring on the prospective memory and control nights in relation to aging

	Prospective memory night		Control night		Inferential statistics		
	Adults <30	Adults ≥30	Adults <30	Adults ≥30	Age correlation	Inter-night correlation	Night effect
Total sleep time (min)	511.50 ± 44.80	426.49 ± 64.48	513.08 ± 41.35	428.63 ± 67.00	$r(74) = -.65, p < .001$	Average ICC = .81, $p < .001$	$p = .74$
Sleep efficiency (%)	92.02 ± 4.81	82.94 ± 10.73	93.20 ± 4.28	83.34 ± 11.46	$r(74) = -.58, p < .001$	Average ICC = .74, $p < .001$	$p = .67$
Sleep onset latency (min)	17.66 ± 14.26	14.79 ± 12.41	13.29 ± 6.78	17.87 ± 22.90	$r(74) < .01, p = .97$	Average ICC = .37, $p = .03$	$p = .68$
Wake after sleep onset (min)	26.88 ± 20.87	72.03 ± 53.36	24.62 ± 25.49	69.80 ± 55.35	$r(74) = .59, p < .001$	Average ICC = .67, $p < .001$	$p = .87$
N1 (min)	26.39 ± 20.17	48.32 ± 34.58	24.86 ± 19.78	37.84 ± 19.00	$r(74) = .43, p < .001$	Average ICC = .86, $p < .001$	$p = .10$
N2 (min)	296.28 ± 43.65	230.62 ± 59.41	300.81 ± 38.24	238.41 ± 51.03	$r(74) = -.60, p < .001$	Average ICC = .71, $p < .001$	$p = .73$
SWS/N3 (min)	78.36 ± 19.78	67.01 ± 40.78	81.14 ± 22.17	70.32 ± 35.63	$r(74) = -.27, p = .02$	Average ICC = .79, $p < .001$	$p = .50$
REM (min)	110.46 ± 24.97	79.38 ± 36.25	106.38 ± 22.24	81.98 ± 31.68	$r(74) = -.52, p < .001$	Average ICC = .75, $p < .001$	$p = .41$
Apnea–Hypopnea Index events/h	0.39 ± 0.91	4.99 ± 6.23	0.36 ± 0.49	4.84 ± 4.77	$r(74) = .60, p < .001$	Average ICC = .77, $p < .001$	$p = .74$

Descriptive data are provided using an age group cutoff of 30 years old, but correlational data relate chronological age as a continuous variable to sleep variables. Sleep variables correlated strongly across the two experimental nights (measured by intraclass correlation [ICC]) and did not differ by condition. Data were missing/corrupted for two control nights.

Ongoing task performance

We first evaluated evening/baseline ongoing task performance, that is, performance before encoding a prospective memory or control task. ANCOVAs on chronological age and condition (prospective memory/control) indicated that evening ongoing task response times and accuracy did not differ across conditions (all Fs ≤ 1.0; Supplementary Table S2). We conducted similar ANCOVAs on morning ongoing task performance, with these data also producing nonsignificant patterns. When averaging ongoing task accuracy across filler/nontarget trials, there were no significant differences between the prospective memory and control conditions in morning ongoing task accuracy ($\text{Ongoing}_{\text{Prospective}}$: M = 0.938, SD = 0.032; $\text{Ongoing}_{\text{Control}}$: M = 0.940, SD = 0.030; $p > .05$) or morning ongoing task response times (responses times were averaged for correct filler trials; $\text{Ongoing}_{\text{Prospective}}$: M = 1043 ms, SD = 300; $\text{Ongoing}_{\text{Control}}$: M = 1001 ms, SD = 308; $p > .05$).

A more complex pattern emerged for mixed ANCOVA analyses that not only included chronological age and condition (prospective memory/control), but also included quartile segments of each ongoing task context (1–4), and controlled for performance on the corresponding evening/baseline ongoing task. For response times (Supplementary Figure S1), there was a significant condition by quartile interaction in the living/nonliving task [$F(3, 210) = 3.32$, MSE = 9452.19, $p < .001$] and the lexical decision task [$F(3, 210) = 3.32$, MSE = 5844.49, $p = .03$], but not the category decision task ($p > .05$) for which there was only a condition main effect [$F(1, 207) = 9.12$, MSE = 10557.04, $p = .004$]. For proportion correct accuracy (Supplementary Figure S2), there was a significant condition by quartile interaction for the lexical decision task [$F(3, 210) = 3.02$, MSE = .001, $p = .03$] and category decision task [$F(3, 207) = 4.93$, MSE = .002, $p = .003$], and a three-way interaction between chronological age, condition, and quartile for the living/nonliving task [$F(3, 207) = 4.78$, MSE = .002, $p = .003$]. The data are illustrated in Supplementary Figures S1 and S2, and collectively they show that there was a mixture of reliance on spontaneous/automatic retrieval and monitoring, consistent with the Multiprocess Framework's account of spontaneous retrieval processes sometimes initiating transient monitoring processes [8, 20].

Prospective memory and control task performance

A mixed ANCOVA on condition and chronological age resulted in a significant interaction for performance on morning control trials versus morning prospective-memory trials, $F(1, 72) = 7.47$, MSE = .06, $p = .008$. Accuracy on the morning control recognition task was high (proportion correct: M = 0.97, SD = 0.06) and age invariant [$r(71) = -.10$, $p = .43$], demonstrating that participants of all ages could easily retain the shape/media and horse/table control words. By contrast, "remembering to remember" to perform an action when seeing the prospective memory cue words was much more difficult for participants (proportion correct: M = 0.53, SD = 0.37), and declined as a function of increasing age, $r(74) = -.34$, $p = .003$ (Figure 2). Prospective memory performance did not significantly differ as a function of ongoing task context or night order counterbalance (Fs < 2.2, ps > .10).

The age effect on prospective memory was still significant when covarying participants' performance during the evening encoding-practice-block to produce a standardized residual score of prospective memory consolidation, $F(1, 73) = 5.48$, MSE = 1.93, $p = .02$ [64]. Furthermore, the age decline in prospective memory consolidation was maintained when statistically controlling for performance on the control recognition task, $F(1, 71) = 7.96$, MSE = 3.04, $p = .006$, ongoing task response times, $F(1, 73) = 4.64$, $p = .03$, and ongoing task accuracy, $F(1, 73) = 9.23$, $p = .003$. Thus, prospective memory consolidation processes decline in older age, even when accounting for age variability in quickly and accurately completing cognitive tasks.

Sleep and prospective memory correlations

When controlling for chronological age, prospective memory consolidation was significantly correlated with REM sleep duration, $r(73) = .32$, $p = .005$ (even following Bonferroni correction). Figure 3 shows the scatterplot between REM sleep duration and prospective memory consolidation, with similar effect sizes across young adults and middle-to-older aged adults. More REM sleep did not simply mean greater vigilant monitoring during the test phase (e.g. ongoing task speed). When controlling for chronological age and evening/baseline ongoing task performance, there was no association between REM sleep

Table 3. Quantitative EEG analyses on the prospective memory night in relation to chronological age and prospective memory consolidation

	Correlation with chronological age	Encoding-adjusted correlation with prospective memory	Age and encoding adjusted correlation with prospective memory
SWA (mean for all electrodes, epochs) μV²/Hz	$r(74) = -.60$, $p < .001$	$r(74) = .18$, $p = .11$	$r_p(73) = .04$, $p = .73$
SO (mean for all electrodes, epochs) μV²/Hz	$r(74) = -.44$, $p < .001$	$r(74) = .10$, $p = .39$	$r_p(73) = -.01$, $p = .91$
Frontal SWA in NREM μV²/Hz	$r(74) = -.61$, $p < .001$	$r(74) = .26$, $p = .03$	$r_p(73) = .13$, $p = .26$
Frontal SO in NREM μV²/Hz	$r(74) = -.55$, $p < .001$	$r(74) = .19$, $p = .11$	$r_p(73) = .06$, $p = .61$
Frontal SWA in SWS μV²/Hz	$r(73) = -.66$, $p < .001$	$r(73) = .23$, $p = .05$	$r_p(72) = .09$, $p = .46$
Frontal SO in SWS μV²/Hz	$r(73) = -.68$, $p < .001$	$r(73) = .22$, $p = .06$	$r_p(72) = .07$, $p = .55$
Frontal spindle density in N2	$r(74) = -.45$, $p < .001$	$r(73) = .15$, $p = .21$	$r_p(73) = .04$, $p = .74$
Frontal spindle density in N3	$r(72) = -.05$, $p = .66$	$r(72) = -.01$, $p = .92$	$r_p(71) = -.03$, $p = .83$

Analyses included delta slow wave activity (SWA, 1–4 Hz), slow oscillations (SO, 0.5–1.0 Hz), and spindle density. Frontal channels included Fp1, Fp2, F3, Fz, and F4. Prospective memory consolidation was operationalized as the standardized residual score of morning prospective memory performance after adjusting for previous night encoding practice block performance.

duration and morning ongoing task response times during the category decision task [r(72) = .06, p = .62], lexical decision task [r(72) = –.08, p = .50], or living/nonliving task [r(72) = –.04, p = .75; see also Supplementary Table S3). Furthermore, the REM–memory relationship did not reflect variability in recent sleep durations. We examined sleep diary and PSG data from participants the night before the prospective memory condition (data available for 64 participants, M = 7.28 h, 15.9% reported napping). After controlling for age, prospective memory performance was not significantly associated with previous-day sleep duration [r(62) = .15] or nap duration [r(62) = –.14]. Thus, recent sleep history did not explain the association between REM sleep and prospective memory consolidation.

Prospective memory consolidation was selectively associated with REM sleep. Table 3 shows that SWA delta power, frontal slow oscillations, NREM spindle density, total sleep time, and AHI were each unrelated to prospective memory consolidation after controlling for chronological age and evening encoding (all ps > .05). Topographic analysis of spindle density from different electrode sites resulted in no significant associations with prospective memory consolidation (Supplementary Figure S3).

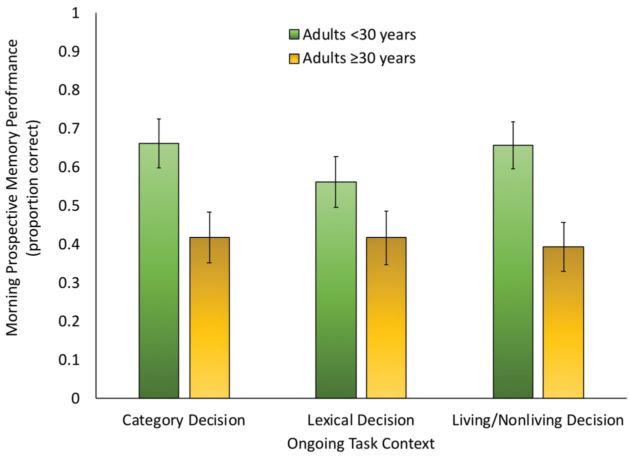

Figure 2. Prospective memory performance decreased with increasing age in all ongoing task contexts (category decision, r = –.29, p = .01, lexical decision, r = –.21, p = .07, living/nonliving decision, r = –.39, p < .001). Morning prospective memory performance is the proportion correct averaged for four trials in each of the three contexts. Error bars reflect standard errors.

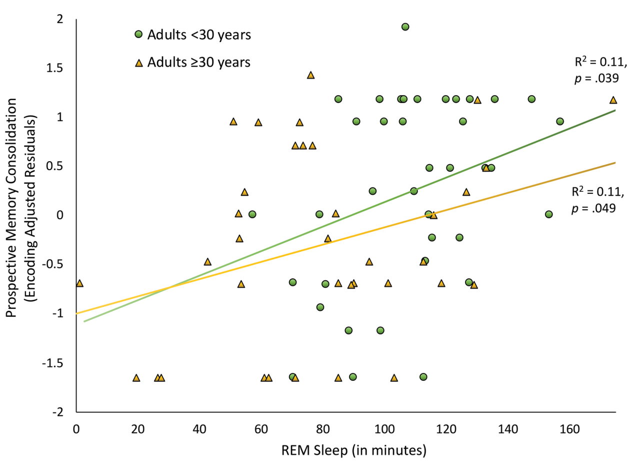

Figure 3. Prospective memory consolidation was associated with previous-night REM sleep duration. Prospective memory consolidation is operationalized as the standardized residuals of morning prospective memory performance after adjusting for evening encoding practice block performance.

Mediation analyses

To test REM sleep duration as a mediator of the effect of aging on prospective memory consolidation, we took a bootstrap estimation approach using 5,000 samples [65]. The unadjusted analysis is illustrated in Figure 4. Consistent with full mediation, when including REM sleep as a mediator, chronological age was no longer a significant predictor of prospective memory performance, b = –.0024, SE = 0.0020, p = 0.25. Bootstrapping analysis showed the indirect coefficient to be significant, b = –.0031, SE = 0.0011 (95% CI = –0.0056 to –0.0012), supporting the hypothesis that REM sleep was a mediator between chronological age and prospective memory performance.

Next, we tested for mediation after controlling for control task and ongoing task performance. Prospective memory was significantly associated with both chronological age, b = –.0056, SE = 0.0022, p = .01, and with REM sleep, b = .0035, SE = 0.0015, p = 0.02. When controlling for REM sleep, chronological age was no longer a significant predictor of prospective memory performance, b = –.0040, SE = 0.0022, p = .08. Bootstrapping showed the indirect coefficient to be significant, b = –.0016, SE = 0.0009 (95% CI = –0.0042 to –0.0004). Furthermore, these results generally replicated even when additionally controlling for several other variables that have been implicated in sleep, cognition, and aging [33], including gender, race/ethnicity, education, MMSE, PRMQ, PSQI, ESS, working memory, fluency, semantic memory, circadian preference, and depression. In this adjusted analysis, prospective memory was significantly associated with REM sleep, b = .0031, SE = 0.0015, p = .046, and age, b = –.0070, SE = 0.0027, p = .01 (after controlling for REM sleep, b = –.0053, SE = 0.0028, p = .06). Even when controlling for these numerous covariates, bootstrapping still showed the indirect coefficient to be marginally significant, b = –.0017, SE = 0.0013 (95% CI = –0.0051 to 0.0000), such that REM sleep accounted for 24.29% of the overall effect [66].

Discussion

Prospective memory consolidation is expected to decline with increasing age, with a significant amount of that decline being mediated by REM sleep. Whereas some previous work found the association between sleep and neurocognitive measures to be weakened with advancing age [33, 67–69], we found

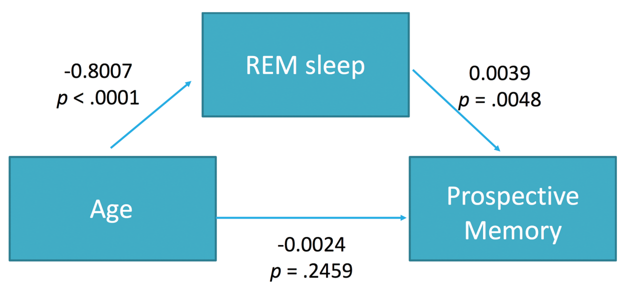

Figure 4. REM sleep duration mediated the effect of age on prospective memory. The values are unstandardized regression coefficients (top) and p values (bottom).

that REM sleep duration was associated with prospective memory consolidation across age groups. Interestingly, we continued to observe this pattern even when controlling for a myriad of variables related to general cognitive functioning, depression, circadian preference, recent sleep quality, and polysomnography-defined total sleep time. In the present work, REM sleep did not simply boost one's attentional ability to vigilantly monitor for prospective memory cues (e.g. ongoing task speed); instead, the collective findings indicated that REM sleep helped preserve the association between *what* needed to be remembered and *when* it needed to be remembered. These findings are consistent with recent theorizing that REM sleep functions to preplay future scenarios so as to promote next-day automatic cognitive processes [27].

There are only two published studies in young adults that examined how sleep physiology related to prospective memory consolidation. In one study, prospective memory did not significantly correlate with any traditional sleep stage parameters [14], and in another study, prospective memory was better following a 3-h early-night sleep interval (SWS-rich) than a 3-h late-night sleep interval (REM-rich) [15]. Rather than contradicting those findings, the differences between our study and previous studies can be understood by the differences in time-in-bed opportunity. The current study included a 9-h time-in-bed opportunity, resulting in an average of 110.5 min of REM sleep. The two published studies included briefer opportunities for sleep, resulting in averages of approximately 75 and 50 min of REM, respectively. Perhaps REM sleep will emerge as a more consistent predictor of memory consolidation if future studies allow for greater variability in REM sleep by extending the time-in-bed opportunity.

Reconsideration of the two-stage/sequential hypothesis of memory processing [70, 71] may unite some of the findings in the sleep and cognitive aging literature. On the one hand, the 50+ year history of neuropsychological studies that related cognitive functioning to polysomnography variables have often reported correlations with REM sleep [33]. In the largest [45] and longest [46] longitudinal studies of polysomnography and cognitive outcomes, low REM sleep predicted more rapid cognitive aging (and SWS did not). Yet, on the other hand, recent cross-sectional studies have suggested that SWA or spindle density mediate age-related decline in memory consolidation [32, 38, 39, 72]. Even more provocative are the findings that experimentally increasing SWA—spindle activity improved memory functioning, at least temporarily, in some older adults [40–42]. In our study of adults aged 18–84, REM sleep was robustly associated with prospective memory, as was frontal SWA (however, SWA was only associated before controlling for chronological age). In weighing all of these findings, our view is that taking an *either*-REM-*or*-SWA approach may be less useful for explaining and remedying the numerous cognitive deficits associated with aging than recognizing that *both* REM *and* SWA contribute, perhaps in a sequential manner [70, 71].

Limitations of this work included a cross-sectional design and a modest sample size (e.g. relatively few middle-aged adults). Sleep and memory studies typically include many statistical tests (as did the current study) [73], but we minimized the chance for false positives by focusing on three empirically based aspects of sleep (REM, SWA, spindles). The REM-memory correlation was significant even with Bonferroni correction, and similar effect sizes were observed in young adults and middle-to-older aged adults [33]. The strength of the age and prospective memory correlation may have been influenced by age differences in optimal time of learning/testing, though statistically controlling for circadian preference did not impact the primary finding that REM sleep duration mediated this age–memory association.

Conclusions

NREM and REM processes may interact dynamically to help preserve a range of cognitive processes [74]. In the current work, REM sleep duration was significantly associated with prospective memory consolidation in young adults and middle-to-older aged adults, which adds to a developing literature on prospective memory being impacted by sleep disruption [9–12, 75–77] and by clinical sleep disorders [78–80]. The current findings fit the theoretical view that prospective memory consolidation occurs via reactivation processes followed by cue–intention association processes, but alternative accounts should also be tested. One alternative account is that cholinergic activity, which promotes both REM sleep [81] and prospective memory [82], is known to decline with aging [44]. Another account is that REM sleep functions to process emotional content [24], and to the extent that an unfinished prospective memory intention is deemed stressful [48], prospective memories may undergo emotional processing during REM sleep. Though there is still much to be learned about how NREM and REM activity interact to preserve brain health and memory functioning [74, 83], the current data indicate that experimentally increasing REM sleep may be a viable next target for combating human errors in "remembering to remember."

Supplementary material

Supplementary material is available at *SLEEP* online.

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