https://doi.org/10.5664/jcsm.9080

JCSM | Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Effects of obstructive sleep apnea on human spatial navigational memory processing in cognitively normal older individuals

Anna E. Mullins, RPSGT, PhD[1,*]; Masrai K. Williams[1,*]; Korey Kam, PhD[1]; Ankit Parekh, PhD[1]; Omonigho M. Bubu, MD, MPH, PhD[2]; Bresne Castillo, RPSGT[1]; Zachary J. Roberts, RPSGT[1]; David M. Rapoport, MD[1]; Indu Ayappa, PhD[1]; Ricardo S. Osorio, MD[2,**]; Andrew W. Varga, PhD, MD[1,**]

*[1]Mount Sinai Integrative Sleep Center, Division of Pulmonary, Critical Care, and Sleep Medicine, Icahn School of Medicine at Mount Sinai, New York, New York; [2]Center for Sleep and Brain Health, Department of Psychiatry, NYU Grossman School of Medicine, New York, New York; *Contributed equally; **Contributed equally as senior authors.*

Study Objectives: Obstructive sleep apnea (OSA) prevalence increases with age, but whether OSA-related sleep disruption could interrupt the processing of previously encoded wake information thought to normally occur during sleep in cognitively normal older adults remains unknown.
Methods: Fifty-two older (age = 66.9 ± 7.7 years, 56% female), community-dwelling, cognitively normal adults explored a 3-D maze environment and then performed 3 timed trials before (evening) and after (morning) sleep recorded with polysomnography with a 20-minute morning psychomotor vigilance test.
Results: Twenty-two (22) participants had untreated OSA [apnea-hypopnea index (AHI4%) ≥ 5 events/h] where severity was mild on average [median (interquartile range); AHI4% = 11.0 (20.7) events/h] and 30 participants had an AHI4% < 5 events/h. No significant differences were observed in overnight percent change in completion time or in the pattern of evening presleep maze performance. However, during the morning postsleep trials, there was a significant interaction between OSA group and morning trial number such that participants with OSA performed worse on average with each subsequent morning trial, whereas those without OSA showed improvements. There were no significant differences in morning psychomotor vigilance test performance, suggesting that vigilance is unlikely to account for this difference in morning maze performance. Increasing relative frontal slow wave activity was associated with better overnight maze performance improvement in participants with OSA (r = .51, P = .02) but not in those without OSA, and no differences in slow wave activity were observed between groups.
Conclusions: OSA alters morning performance in spatial navigation independent of a deleterious effect on morning vigilance or evening navigation performance. Relative frontal slow wave activity is associated with overnight performance change in older participants with OSA, but not those without.
Keywords: elderly, learning, EEG, SWA, Alzheimer disease
Citation: Mullins AE, Williams MK, Kam K, et al. Effects of obstructive sleep apnea on human spatial navigational memory processing in cognitively normal older individuals. *J Clin Sleep Med*. 2021;17(5):939–948.

BRIEF SUMMARY
Current Knowledge/Study Rationale: Understanding the impact of obstructive sleep apnea on cognitive function in older adults is clinically important and may shed light on biological mechanisms by which sleep serves to process previously encoded wake information.
Study Impact: This study indicates that obstructive sleep apnea can negatively impact sleep-dependent cognitive processing of a spatial navigation task, even when obstructive sleep apnea is mild on average, without negatively impacting morning psychomotor vigilance. Slow wave activity appears to be an important marker of the brain's ability to process and utilize spatial information encountered during prior wakefulness in older individuals with obstructive sleep apnea.

INTRODUCTION

Sleep is known to be important for memory processing.[1,2] The mechanisms detailing how different sleep stages contribute to memory formation are not well delineated,[3] but neural oscillations characteristic of non–rapid eye movement (NREM) sleep such as slow wave activity (SWA) are thought to mediate learning.[4] This theory is supported by findings showing learning-dependent increases in SWA[5] during sleep in healthy individuals.

It follows then that disorders causing sleep disruption, such as obstructive sleep apnea (OSA), could compromise the stability of these oscillations, and offline memory processing would be impaired. During daytime neuropsychological testing, OSA has been associated with deficits in tasks involving executive functioning,[6] and in older adults, OSA is associated with an increased risk of developing Alzheimer disease[7–11]. Nevertheless, a causal relationship between OSA, cognitive decline, and Alzheimer disease is not firmly established.[12] Most studies investigating cognitive function in OSA assess general cognitive abilities during daytime testing or neurobehavioral vigilance rather than overnight memory processing involving encoding and recall components separated by a period of sleep.[2] A small number of studies incorporating sleep-related memory assessments in OSA patients have demonstrated impaired processing of declarative and procedural memory tasks compared to healthy controls,[13,14] but the memory-encoding components and implicit motor memory formation appeared intact.[15] In a series of studies showing impaired overnight motor sequence task learning in moderately severe OSA, a negative relationship was observed between task performance and a polysomnographic (PSG) arousal index,[16,17] with the later

study showing increasing age to be associated with fewer overnight improvements.

Some features of sleep which are disrupted by OSA could be important for memory processing. Slow waves and SWA are in the frequency range of ~0.3 to 4 Hz and encapsulate both slow oscillations (SOs) of ~1 Hz and delta band activity between ~1 and 4 Hz,[18,19] and it may be important to functionally differentiate SOs from delta activity, as they have been shown to have differing impacts on both memory (in rodents)[20] and cortical amyloid deposition.[21] In cognitively normal individuals, reductions in SWA and SOs during NREM sleep are associated with biomarkers of Alzheimer disease[9,21–23] and impairments in declarative memory.[21,22]

Spatial navigational memory is defined as the ability to recall routes to salient targets in novel environments. This type of memory is particularly important because impairments in spatial navigational memory are universally present in those with bona fide Alzheimer disease. Furthermore, impaired spatial navigational memory in otherwise cognitively normal older individuals is thought to be a potential risk factor for subsequent Alzheimer disease.[24,25] Much of the research concerning sleep and memory in rodents utilizes hippocampus-dependent spatial learning paradigms where replay of hippocampal place-cell sequences during sleep, particularly during sharp-wave ripples, is thought to contribute to the offline processing of spatial information.[26–28] In humans, overnight sleep enhances performance on a virtual maze navigation task that is not observed after a comparable awake period in daytime.[29,30] Furthermore, overnight improvements in spatial navigation on this task are attenuated in older compared to younger adults, and are positively associated with relative frontal SWA.[31] The benefits of overnight sleep for improvements on this task are also attenuated when OSA is induced specifically during rapid eye movement (REM) sleep in continuous positive airway pressure–treated patients.[32]

OSA is quite common in older individuals with several studies reporting that up to half of older adults aged > 60 years have at least mild OSA,[33] often without significant daytime sleepiness.[8] It is important to define whether such highly prevalent OSA has an impact on immediate memory on a sleep-mediated memory task and, if so, presents a possible risk for future cognitive decline. Therefore, it is critical to define cognitive implications of OSA beyond sleepiness. The present study investigates whether OSA in older individuals results in impaired sleep-mediated spatial navigational memory performance or influences measures of sleep continuity and slow wave activity. Based on previously demonstrated associations between sleep continuity and frontal slow wave activity with overnight change in spatial memory performance,[31] we hypothesized that SWA or slow wave continuity in older adults with and without OSA would be predictive of overnight performance change.

METHODS

Participants

Sixty-one (61) adults were recruited from a pool of healthy older adults participating in National Institutes of Health–supported longitudinal studies on normal aging and Alzheimer disease at New York University. All participants aged between 55 and 85 years had ≥ 12 years of education, were considered cognitively normal based on clinical neurological and neuropsychological assessment (including the Clinical Dementia Rating scale and Mini-Mental State Exam), and were judged to be nondepressed (as defined by Geriatric Depression Scale < 6).

Exclusion criteria were the use of any psychoactive drugs [aside from the stable (> 8 weeks) use of a single selective serotonin reuptake inhibitor antidepressant], the presence of unstable comorbid conditions (stroke, uncontrolled diabetes, traumatic brain injury, lung diseases, drug abuse, or magnetic resonance imaging evidence of intracranial mass or infarcts), or the presence of circadian rhythm disorder. An Epworth Sleepiness Scale was completed by participants at this time to assess self-reported sleepiness. The Epworth Sleepiness Scale is a behavioral sleepiness questionnaire using a 4-point introspective self-rating scale to assess the hypothetical chance of dozing across 8 different situations "during recent times." Higher values represent greater self-reported sleepiness, where the cut-off of ≥ 10 points is accepted to indicate excessive daytime sleepiness.[34] OSA, defined as an apnea-hypopnea index (AHI) with 4% desaturation criteria for hypopnea (AHI4%) ≥ 5.0 events/h, was present in 23 people, and no OSA (AHI4% < 5.0 events/h) was observed in 38 individuals. All participants provided informed consent prior to their participation in the study where they underwent in-lab polysomnography, maze testing, and psychomotor vigilance testing (PVT). All procedures were approved by both the New York University Langone School of Medicine and Icahn School of Medicine at Mount Sinai Institutional Review Boards.

Virtual maze performance and psychomotor vigilance test

At about 20:00 on each night of the study, participants began training on a virtual maze task, a simple 3-D environment designed for this research.[30] After a period of general familiarization with joystick controls (Thrustmaster™, Guillemot Corporation, Carentoir, France) in a virtual Z-shaped corridor, participants initially spent 5 minutes exploring a complex maze designed using "Unreal Tournament 3 Editor" (Epic Games, Cary, NC). Avatar walking speed and turning speed were reduced to minimize motion "cybersickness." The game was projected onto a screen in a darkened testing room. The viewing area was 67 × 50 inches, and participants sat 13 feet away with their vision corrected if they usually required it. Participants were instructed to remember the layout of the maze environment as well as possible. Subsequently, participants navigated through the same maze during 3 presleep test trials, in which they were instructed to reach a specified goal point as quickly as possible. Time to reach the goal per trial was capped at 10 minutes (600 seconds). Nine (9) participants (1 with OSA and 8 without OSA) who failed to reach the goal after 10 minutes in 2 or more of the 3 evening presleep maze trials were excluded from analysis per our findings from a previous publication showing older and younger adults encode similarly if individuals failing 2 or more trials were excluded.[31] This resulted in a total of 52 participants included in the final analysis.

Participants performed a standardized 20-minute psychomotor vigilance test (Ambulatory Monitoring Inc, Ardsley, NY) beginning 1 hour after awakening at their habitual wake time. Thereafter, they performed 3 postsleep test trials on the 3-D virtual maze, again instructed to reach the same specified goal point as quickly as possible.

The primary performance metric on the virtual maze was completion time (CT). CT was recorded by the software to a log file that was saved after each trial. Additionally, the countdown timer at the point of maze completion was manually recorded by the technician administering the task. In addition to individual completion time per trial, overnight change was calculated as the difference between the average of the 3 trials before and after sleep as a percentage change. This measure has the advantage of normalizing any differences between participants in navigation speed (for example due to proficiency with using the joystick). Positive values represent improvement and negative values represent worsening after sleep.

Psychomotor vigilance test metrics included *mean reaction time* (in milliseconds) and *number of lapses* (no response after 500 milliseconds). Participants also self rated pre- and post-PVT sleepiness using a 1–10 scale (where 1 corresponded to "not sleepy" and 10 "very sleepy"). A transform of the number of lapses was done to enable parametric testing [Lapses (transform) = sqrt (#lapses) + sqrt (#lapses+1)].[35] PVT was not completed for 3 participants without OSA. In 1 case, this was due to a device malfunction. In the other 2 cases, the PVT was omitted from the protocol to cater to participants who were short on time in the morning before needing to leave the sleep lab.

Polysomnography

A full-night, attended in-laboratory PSG was acquired following standard American Academy of Sleep Medicine criteria[36] at the Mount Sinai Integrative Sleep Center using Compumedics E-series (Melbourne, Australia). Participants were connected to PSG and lights off was scheduled to approximate the participant's self-reported habitual bedtime. Prior to this a bedtime questionnaire was completed by participants recording information on activities such as caffeine, alcohol, and food and drug intake for that day. Signal acquisition included electroencephalography (EEG: F3, F4, C3, C4, O1, O2), left and right electro-oculography, all sampled at 256 Hz and referenced to the contralateral mastoid (M1, M2), submental bipolar electromyography, respiration by a nasal cannula/pressure transducer and oral thermistor, effort by rib/abdomen impedance plethysmography; single-channel electrocardiography, and oxygen saturation by pulse oximetry. PSGs were scored in 30-second epochs according to standard criteria[37] for sleep and EEG arousals. Total sleep time and percent time spent in wake, REM sleep, non-REM stage 1 (NREM 1), non-REM stage 2 (NREM 2), and slow wave sleep (SWS) were determined. Respiratory events were scored from the airflow signal using American Academy of Sleep Medicine criteria and stage-specific (Total, REM, and NREM) apnea indices were calculated. Apneas were defined as absence of airflow for ≥ 10 seconds. Hypopnea 4% was defined as a reduction in the amplitude of breathing by 30% or more for ≥ 10 seconds with ≥ 4% decline in blood oxygen saturation, irrespective of the presence of an arousal. Hypopnea (3% or arousal) was defined as a reduction in the amplitude of breathing by 30% or more for ≥ 10 seconds accompanied by ≥ 3% decline in blood oxygen saturation or EEG arousal. The AHI4% was defined as the sum of all apneas and hypopneas with ≥ 4% desaturation divided by the total sleep time in hours. The AHI3A was defined as the sum of all apneas and hypopneas with ≥ 3% desaturation or EEG arousal divided by the total sleep time in hours. All PSGs were scored by 1 of 2 RPSGTs (B.C. or Z.J.R.) and all PSGs were reviewed by a single expert (I.A.) for consistent respiratory event scoring.

Sleep continuity was assessed 2 ways. Average sleep bout length was calculated from the hypnogram by assessing the mean length in minutes of contiguous epochs (30 seconds) of sleep scored as that stage, terminated by one or more epochs scored as another stage, including wake. Secondly, survival curve analysis for sleep continuity was performed for each sleep stage (REM, NREM 1, NREM 2, and SWS) using a bootstrap-based technique that accounts for the number of contiguous epochs (30 seconds) contributed by each participant for each sleep stage.[32,38]

Quantitative EEG analysis

Frontal EEG channels (active electrode referenced to contralateral mastoid, ie, F3-M2 and F4-M1) were decomposed into oscillatory and nonoscillatory or transient components using our previously published DETOKS method.[39] Absolute SWA and SO power was calculated using the average power density by fast Fourier transform in the 0.5–4 Hz and 0.6–1 Hz frequency ranges, respectively. Relative SWA and SO activities were defined as the absolute SWA or SO power divided by the absolute spectral power across all frequencies (0.5–50 Hz and 0.6–50Hz) for a given EEG derivation, allowing normalization across participants of spectral power that may otherwise have been influenced by interindividual anatomical differences. Average frontal EEG measures for relative SWA and SO power were calculated [eg, (F3-M2 + F4-M1)/2] for each participant and used in all subsequent analyses. Where visual inspection by an experienced PSG technologist (AEM) indicated > 20% of the recorded EEG signal contained artifact, that EEG derivation was removed from further analysis. Quantitative EEG (qEEG) analysis for frontal signals were not averaged for 1 participant without OSA due to poor F3-M2 signal quality. Instead qEEG measures from the F4-M1 signal were used. EEG analysis were conducted blind to the participant's OSA status and performance measures.

Data analysis

Data were analyzed and plotted using SigmaPlot version 12.0 (Systat Software, San Jose, CA), IBM SPSS Statistics for Windows, Version 24 (IBM Corp., Armonk, NY), MATLAB Release 2017b (The MathWorks, Inc., Natick, MA), and RStudio Version 1.1.456 using the package ggplot2.[40] Comparisons of sleep and psychomotor vigilance data were performed between participants according to OSA status using unpaired *t* tests for normally distributed data, and mean and standard deviation values are reported. For data not normally distributed, analysis consisted of Wilcoxon signed-rank tests

and median and interquartile range values are reported. Results for all statistical analyses were considered significant at $P < .05$. Kolmogorov-Smirnov tests were used to compare survival curve distributions of OSA vs non-OSA.

For maze performance data, OSA group differences in percent of change overnight in completion times was assessed with a *t* test. Additionally, trial-by-trial analyses of completion time pre- and postsleep were conducted using a 2-way mixed factorial analysis of variance with OSA status as the between-participants independent variable and trial number as the within-participants independent variable. Average completion time data were natural log transformed to overcome violation of Levene's test of equality of variances prior to analysis.

Bivariate and partial Spearman's correlations between overnight change in maze completion time and sleep continuity and relative frontal SWA/SO power measures were conducted for all participants and according to OSA status with age and sex as covariates.

RESULTS

Demographics, sleep architecture, and continuity

The average age of the participants was 66.9 ± 7.7 years, and 29 (56%) were female. There were no significant differences in age or sex, but individuals with OSA had a significantly higher body mass index than those without OSA. Participants were majority college-educated and displayed no global cognitive impairments according to the Mini-Mental State Exam. There were no significant differences between those with and without OSA for years of education or Mini-Mental State Exam scores. There were no significant differences in total sleep time or sleep efficiency according to OSA status. By definition there were significant differences in severity of OSA measured by the AHI4% and the AHI3A criteria, and the total arousal index was significantly increased in participants with OSA. Of note, OSA severity in those participants with OSA was mild on average (median AHI4% = 11.0 events/h, range 0–59.7). Participants with OSA had a significantly higher percentage of NREM 1 sleep, but we observed no significant difference in percentage of NREM 2 or REM. SWS percentage in older participants with OSA (median SWS% = 12.6, range 1.0–32.4) was also not significantly different compared to older participants without OSA (median SWS% = 15.2, range 3.4–39.8). These results are summarized in **Table 1**.

Sleep continuity in terms of mean sleep bout length of any sleep stage was not significantly different between the 2 groups. However, the cumulative probability distribution curves for REM (**Figure 1A**) and NREM 2 sleep (**Figure 1C**) in participants with OSA was significantly left-shifted ($P < .0001$), indicating smaller cumulative bout durations and thus more REM and NREM 2 sleep fragmentation in participants with OSA compared to those without OSA. The cumulative duration probability distribution for SWS in participants with OSA was significantly right shifted ($P < .05$), indicating larger cumulative bout durations and less SWS fragmentation in participants with OSA compared to those without (**Figure 1D**). We performed a sensitivity analysis to ensure this effect was not driven by an outlier with OSA who had a particularly long SWS bout (~30 minutes), which was 3 times that of the longest SWS from any other participant. The cumulative probability distribution of SWS remained significantly right-shifted when this participant was excluded. There were no significant differences in the cumulative duration probability distribution of NREM 1 sleep (**Figure 1B**).

Effects of OSA on spatial navigational memory and psychomotor vigilance

Overnight percent change in maze completion time was not statistically different between participants with and without OSA (OSA: –6.4% vs no OSA: +5.2%, $P = .35$; unpaired *t* test) (**Figure 2**).

When we tracked participants' average maze completion time across trials before sleep, there was no main effect of trial number ($F_{(1,50)} = 0.3$, $P = .9$), no main effect of OSA status ($F_{(5,50)} = 0.02$, $P = .9$), and no interaction between these variables ($F_{(5,50)} = 1.6$, $P = .16$.) However, when we examined maze completion times after sleep, we observed a significant interaction between postsleep trials (4–6) and OSA status group ($F_{(2,50)} = 3.53$, $P = .03$), such that participants without OSA continued to get faster (shorter completion times) across morning trials while participants with OSA took progressively longer to find the target on successive morning trials (**Figure 3**). Holm-Sidak posthoc analysis showed that within trial 6, participants with OSA had significantly slower completion time compared to those without OSA ($P < .05$).

There were no significant differences observed in participants with OSA compared to those without for PVT mean reaction time (OSA = 259 ms vs non-OSA = 277 ms, $P = .08$; Wilcoxon signed-rank test) or PVT lapses (OSA = 3.2 vs non-OSA = 3.7, $P = .09$; Wilcoxon signed-rank test) (**Figure 4**).

There were no significant differences between the groups in sleepiness prior to the morning PVT (OSA = 3.5 vs non-OSA = 2.0, $P = .22$; Wilcoxon signed-rank test) but afterwards participants with OSA rated themselves significantly sleepier than those without OSA (OSA = 5.5 vs non-OSA = 2.0, $P = .01$; Wilcoxon signed-rank test) (**Figure 5**).

Sleep architecture correlates of spatial navigational memory performance

There were no significant associations between NREM2, REM, or SWS bout length and overnight change in spatial navigation maze performance. Similarly, no significant relationships were observed between arousal index and overnight change in maze completion time.

We did not observe any differences in relative frontal SWA (OSA = 70.9 μV^2 vs non-OSA = 71.1 μV^2, $P = .84$; Welch 2-sample *t* test) or SO power (OSA = 26.0 μV^2 vs non-OSA = 24.2 μV^2, $P = .11$; Welch 2-sample *t* test) according to OSA status.

There was no significant association between change in overnight percent change in maze completion time and SWA (rho = 0.2, $P = .09$) or relative frontal SO power (rho = –0.01, $P = .94$) among all participants. However, frontal SWA positively correlated with overnight change in maze completion time where greater relative frontal SWA was associated with

Table 1—Participant demographics and polysomnographic variables.

	All Participants (n = 52)	Non-OSA (n = 30)	OSA (n = 22)	Significance
Age, years	66.9 ± 7.7	66.8 ± 8.8	67.1 ± 6.3	.88
Sex, female/male	29/23	18/12	11/11	.41
Race, Black/White	8/44	4/26	4/18	.65
Ethnicity, Hispanic/non	3/49	1/29	2/20	.40
BMI, kg/m^2	27.0 ± 5.4	24.6 ± 4.3	30.2 ± 5.2	< .001**
ESS/24	5 (4)	4.5 (6.8)	5.5 (3.0)	.39
Education, years	16 (4)	16 (3.5)	18 (4)	.87
Mini-Mental State Exam/30	29 (2)	29 (1)	29 (2)	.56
AHI4% (per hour)				
Total	3.1 (9.0)	0.5 (1.6)	11.0 (20.7)	< .001**
REM	2.8 (16.7)	1.3 (2.6)	25.4 (31.8)	< .001**
NREM	1.9 (7.1)	0.3 (1.1)	11.0 (22.7)	< .001**
AHI3A (per hour)				
Total	12.2 (14.9)	5.4 (4.9)	21.2 (20.3)	< .001**
REM	10.8 (24.3)	7.6 (7.7)	38.3 (34.8)	< .001**
NREM	8.9 (14.8)	3.7 (4.8)	20.1 (24.8)	< .001**
SpO_2 nadir (%)				
REM	88 (8)	91.0 (5.5)	82.0 (9.3)	< .001**
NREM	89 (8)	90.0 (3.8)	83.5 (8.5)	< .001**
Time in bed, minutes	448.3 ± 56.4	452.2 ± 61.0	443.0 ± 50.4	.55
Total sleep time, minutes	365.1 ± 66.4	360.3 ± 71.5	371.7 ± 59.8	.53
Sleep efficiency, %	84.8 (11.1)	84.8 (10.0)	84.0 (10.6)	.75
Sleep onset latency, minutes	7.2 (7.8)	6.4 (7.0)	9.0 (8.6)	.92
WASO, % TSP	14.4 (10.3)	15.9 (12.1)	12.4 (6.9)	.19
REM, % TST	18.8 ± 5.8	19.3 ± 6.2	18.1 ± 5.4	.49
NREM 1, % TST	17.7 (15.5)	16.4 (8.0)	23.5 (10.8)	.02*
NREM 2, % TST	46.7 ± 9.4	48.3 ± 9.0	44.6 ± 9.6	.17
SWS, % TST	13.7 (11.2)	15.2 (12.6)	12.6 (7.9)	.53
Arousal index, total	14.7 (10.5)	13.1 (10.5)	21.8 (17.0)	< .001**
Average bout length (minutes)				
REM	7.7 (7.0)	7.2 (7.4)	8.4 (2.5)	.97
NREM 1	1.0 (0.3)	1.0 (0.3)	1.0 (0.4)	.84
NREM 2	2.7 (1.5)	3.1 (2.1)	2.2 (1.7)	.07
SWS	2.4 (4.4)	2.3 (3.2)	2.5 (3.1)	.58

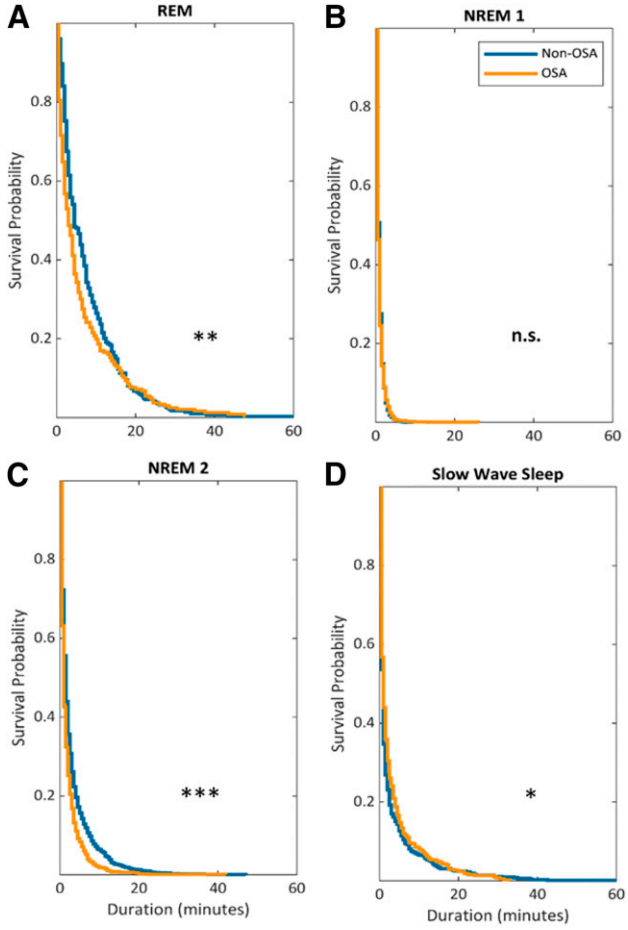
Values are mean ± SD or median (interquartile range). *P < .05, **P < .001. AHI3A = apnea-hypopnea index (hypopnea 3% O_2 desaturation/EEG arousal criteria), AHI4% = apnea-hypopnea index (hypopnea 4% O_2 desaturation criteria), BMI = body mass index, EEG = electroencephalogram, ESS = Epworth Sleepiness Scale, NREM 1 = non-REM stage 1 sleep, NREM 2 = non-REM stage 2 sleep, OSA = obstructive sleep apnea, REM = rapid eye movement sleep, SpO_2 = peripheral capillary oxygen saturation, SWS = slow wave sleep, TSP = total sleep period, TST = total sleep time, WASO = wake after sleep onset.

better overnight maze performance in OSA participants only (r = .51, P = .02) (**Figure 6**). This association remained the same after controlling for age and sex.

DISCUSSION

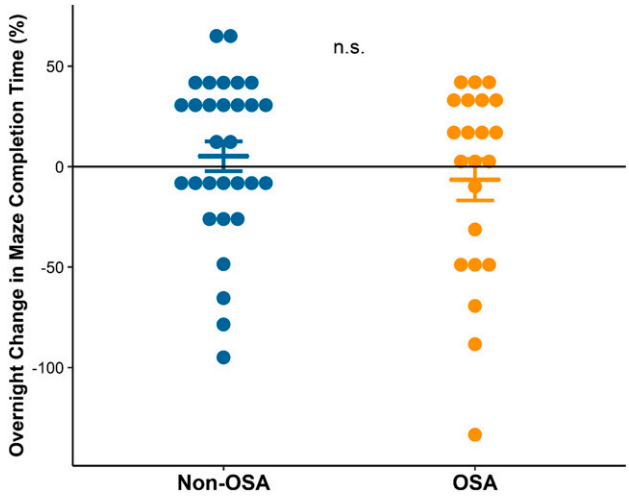
The current work suggests OSA significantly impacts the pattern of morning performance on a spatial navigation task without influencing evening encoding in cognitively normal older individuals. Although we lack a full mechanistic understanding of the offline processing of spatial information, hippocampal place cells activated during encoding in rodents have been found to be reactivated in a similar temporal sequence during the depolarized up states of SOs during sleep,[28] a phenomenon thought to at least partially underlie sleep's role in memory. OSA, with its associated sleep fragmentation and intermittent hypoxia, can short-circuit such replay phenomena, which would be hypothesized to thus negatively impact the subsequent recall of the information encoded before sleep.[27]

Figure 1—Sleep fragmentation assessed using cumulative duration probability distribution shows stage-specific differences according to OSA diagnosis.



Survival curves (cumulative probability distributions) of stage-specific sleep runs in non-OSA (blue) and OSA (orange). The survival curves showed a significant shift toward less continuous REM (**A**) and NREM 2 (**C**) sleep bouts in OSA (orange) compared with non-OSA (blue), and more continuous SWS (**D**) in OSA compared to participants without OSA (***P < .00001, **P < .0001, *P < .05, n.s. = not significant, log-rank test). No significant difference between groups was observed in the survival curves for NREM 1 (**B**). NREM = non–rapid-eye movement, OSA = obstructive sleep apnea, REM = rapid eye movement, SWS = slow wave sleep.

Figure 2—Overnight change in spatial navigation completion time is not different according to OSA diagnosis.



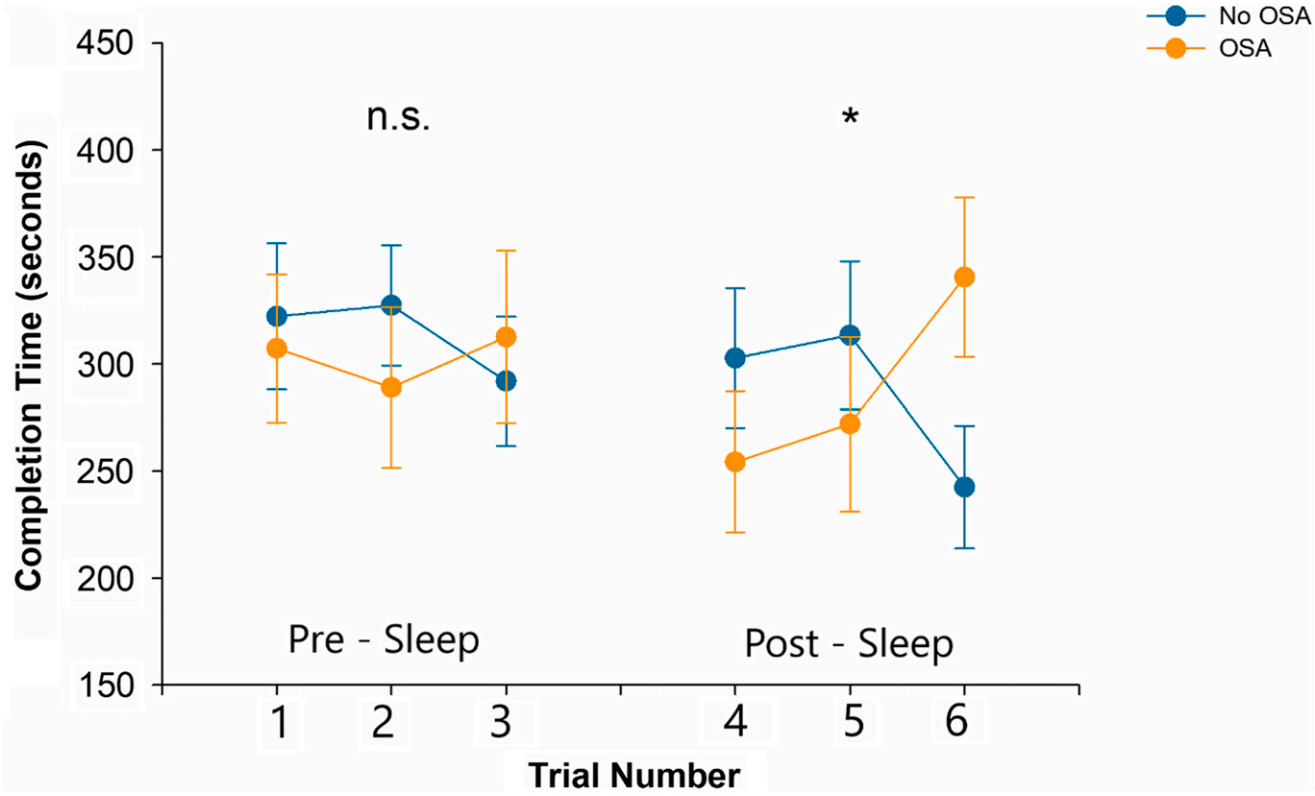
Overnight change in maze completion time was not statistically different between older participants with (orange) and without (blue) OSA. Crossbars represent mean and standard error values. n.s. = not significant, OSA = obstructive sleep apnea.

Hippocampal pyramidal cells (eg, place cells) are known to be particularly sensitive to sustained hypoxia, but effects of intermittent hypoxia are less studied. Since sleep is thought to be important for the processing of memories encoded during prior wakefulness, we argue that behavioral paradigms in which encoding and retrieval of memories are separated by a period of sleep that either does or does not contain significant OSA are particularly salient for elucidating effects of OSA on memory.[2] Experiments that have employed such a paradigm have demonstrated a deleterious effect of OSA on visual declarative memory,[13] 2-D spatial card-matching memory, verbal memory,[41] and forms of motor memory, including mirror tracing,[13] the serial reaction time test, and motor sequence task.[14,16] The 2 research groups using the motor sequence task conducted follow-up studies investigating OSA treatment and found longer-term use, but not a single night of continuous positive airway pressure therapy, augmented offline sleep-dependent motor memory consolidation.[42,43]

Although we speculate it is possible that OSA impacts the processing of previously encoded information during sleep, the difference in the pattern of morning performance could also arise from alternative mechanisms. Even memories that are appropriately consolidated after encoding could be altered by the act of recall itself. The memory reconsolidation theory posits that reactivation of memories (which would occur on the first morning spatial navigation trial) make the memory labile, at which point the memory can be reconsolidated or degraded.[44] Memory reconsolidation has been shown to depend on protein synthesis, and research has shown that acute periods of sleep disruption negatively impact key molecular pathways that govern protein synthesis.[45,46] It is therefore possible that sleep disruption resulting from OSA negatively impacts the reconsolidation process by limiting the protein synthesis resources needed for such reconsolidation, leading to a continual decline in performance after the spatial memory has been made labile by its reactivation during the first morning trial.

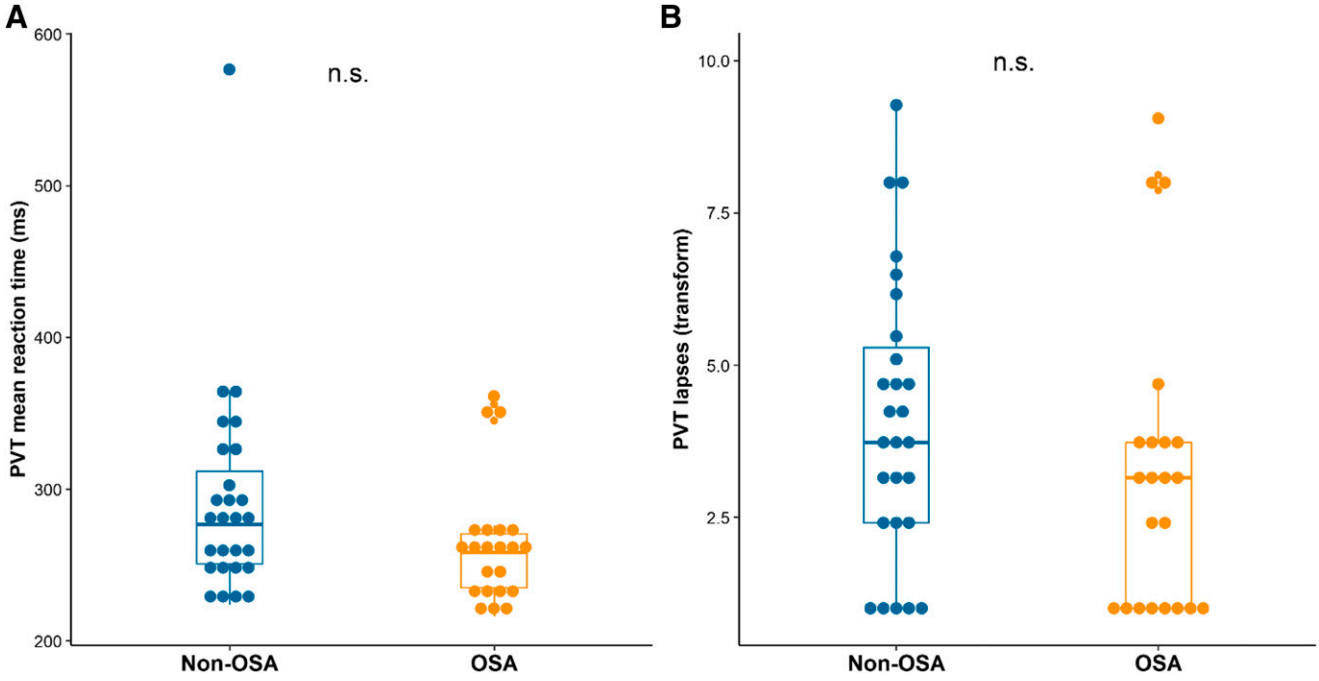
A deleterious effect of OSA on spatial navigational memory has been previously demonstrated when OSA was induced by selective continuous positive airway pressure withdrawal during REM sleep in participants with severe OSA who were on average 54 years old.[32] In that work, mean bout length of REM sleep significantly predicted overnight change in maze performance, a relationship we did not observe in the current work. While the cumulative probability distribution analysis of REM did indicate a significant left shift, REM bout length was not significantly different between participants with and without OSA, a phenomenon likely related to the overall mild severity of

Figure 3—Spatial navigation completion time changes across trials.



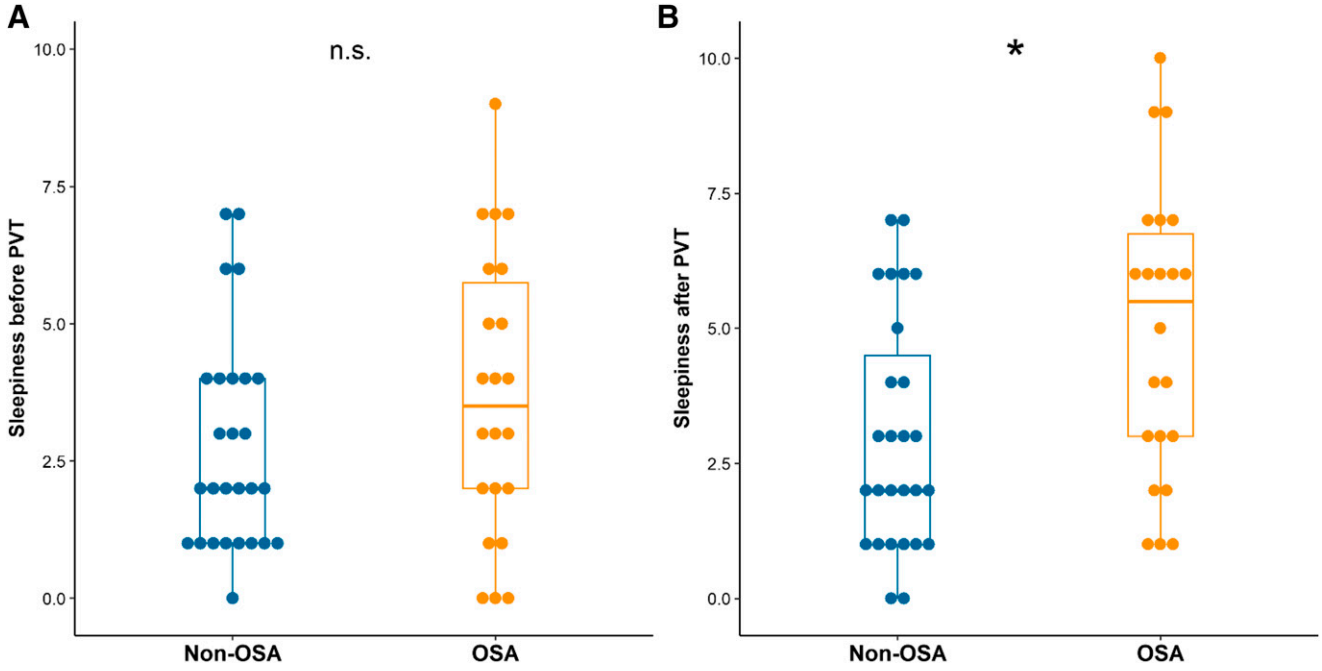
There were no significant differences in presleep maze completion times (trials 1–3) or postsleep maze completion times (trials 4–6) between those with (orange) and without (blue) OSA. However, there was a significant interaction between OSA group and morning postsleep trial number (2-way repeated measures analysis of variance). n.s. = not significant, *P < .05, OSA = obstructive sleep apnea.

Figure 4—There were no significant differences in PVT reaction time or lapses between participants with and without OSA.



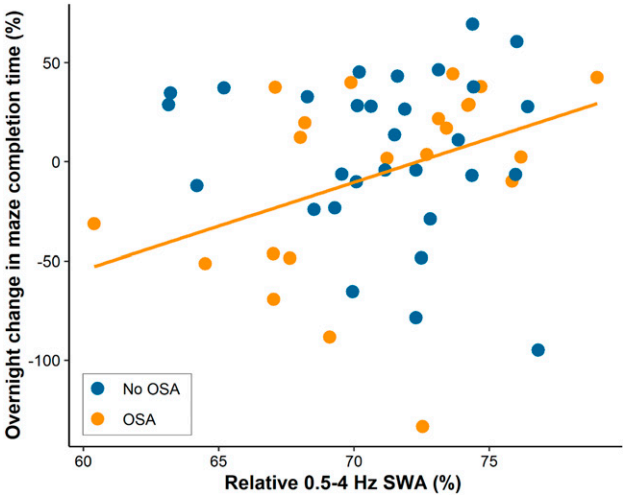
There were no significant differences between participants with OSA (orange) and participants without OSA (blue) for mean reaction times (**A**) and lapses (reaction time > 500 ms) (**B**) during the morning PVT. Box and whiskers represent median and interquartile range values. n.s. = not significant, OSA = obstructive sleep apnea, PVT = psychomotor vigilance testing.

Figure 5—More self-reported sleepiness in participants with OSA after 20-minute psychomotor vigilance testing.



Participants with OSA (orange) reported significantly greater sleepiness after PVT (**B**) but not before PVT (**A**) than participants without OSA (blue). Box and whiskers represent median and interquartile range values. n.s. = not significant, *P <.05, OSA = obstructive sleep apnea, PVT = psychomotor vigilance testing.

Figure 6—Greater SWA in OSA is associated with better overnight maze completion time performance.



Greater relative SWA (0.5–4 Hz) during NREM sleep at frontal electroencephalogram positively correlates with better overnight maze performance improvements in participants with OSA (r = .51, P = .02) but not in those without OSA. A negative value for overnight change indicates slower, on average, postsleep maze completion times compared to presleep completion times. NREM = non–rapid eye movement, OSA = obstructive sleep apnea, SWA = slow wave activity.

OSA in those with OSA. An additional possible reason for these different findings is the differing research designs. The previous finding of a relationship between REM sleep consolidation and maze performance was a within-participants design where apnea-induction was specific to REM sleep and the degree of recapitulated OSA in REM was severe. The importance of REM sleep for forms of spatial memory is underscored by work in rodents, where optogenetic suppression of hippocampal theta rhythm during REM (but not NREM) impaired learning of spatial object placement.[47] When disruption of REM stems from OSA, there may be indirect effects on cognition stemming from adverse cardiovascular and metabolic outcomes in addition to direct impacts on neurophysiology.

OSA is very common in older individuals: About 50% of participants aged > 60 years have an AHI3A ≥ 15 events/h, though often without the same associated daytime sleepiness seen in younger individuals.[8] It bears noting that the individuals in this study were recruited from the community, rather than a sleep clinic, had few sleep complaints, and in most cases were unaware of OSA diagnosis. They also reported low levels of sleepiness (average Epworth Sleepiness Scale 5/24), and although OSA is often associated with daytime sleepiness, participants with OSA in this study were not significantly more sleepy than those without OSA. We did not observe any significant differences in morning PVT performance in those with OSA compared to those without OSA. The PVT is an important control measure, and the results of this study indicate impaired vigilance or inattention resulting from OSA is unlikely to explain the observed differences in morning performance of the spatial navigation task. However, there is the possibility of increased sleepiness or fatigue related to time on task in those with OSA, as indicated by the significantly higher levels of self-reported sleepiness reported on average by these participants after but not before completion of the PVT in spite of equivalent mean reaction time and number of lapses during the PVT itself.

This possibility of increased fatigue with time on task is potentially supported by the observation that the pattern of performance in participants with OSA shows a worsening of performance across the postsleep trials. Perhaps those with OSA experienced greater working memory resource depletion after the PVT and the higher cognitive load of the maze task directly following this[48] resulted in both diminishing motivation and capacity for the level of effort required to find the target.[49] However, support for this explanation is found only in younger individuals without sleep disorders.

The fact that OSA was mild on average in the cohort of older participants (with only 8/22 participants having moderate to severe OSA) is worth emphasizing. Debate remains about the need to treat mild OSA, particularly when common symptoms of OSA such as daytime sleepiness or snoring are absent. The current findings suggest at least that there may be a consequence of OSA on memory in cognitively normal older individuals without sleep complaints. We acknowledge it is difficult to determine whether the findings would generalize to those individuals seeking treatment for OSA in a clinical setting. Such individuals often have daytime sleepiness, which could potentially worsen performance on morning memory testing even beyond what is observed here. That said, there is evidence that older participants experience less sleepiness from equivalent levels of OSA than younger participants do.[50] Whether such an effect of OSA on spatial memory can be ameliorated by treatment of OSA with continuous positive airway pressure or other means remains to be explicitly tested.

Slow wave sleep may be important for spatial navigation memory processing. We previously observed a positive association between relative frontal SWA and overnight maze performance in younger and older cognitively normal adults without OSA,[31] and the degree of blood flow to the right hippocampus during SWS predicted offline change in a spatial navigation task.[51] Here we observe a positive association between overnight percent change in completion time and relative frontal SWA in those with OSA, a relationship which did not change markedly after controlling for age and sex. While reduced SWS and SWA can be observed in OSA, the relationship between OSA severity and measures of slow wave sleep is likely to be nonlinear, and cortical EEG responses (including K-complexes) to respiratory events during sleep within individuals have been variable.[52] Indeed, large-scale studies where EEG microstructure is well characterized in OSA are lacking.[53] In this study, we feel the likelihood is low that OSA-mediated changes in measures of slow wave sleep account for the differences in spatial navigation performance, given that we did not observe significant differences in SWS duration or bout length. We also observed a small but statistically significant right shift in the cumulative probability distribution for SWS in participants with OSA, indicating increased probability for midrange SWS bout duration; we feel this would be unlikely to negatively impact memory processing but may be involved in these participants' resilience to sleepiness.

Acknowledged limitations of the study include the lack of a priori case-control design or counterbalance between the order of the morning PVT and maze task administration. Although only a single spatial navigation memory task (plus PVT) was assessed at the time of the in-laboratory PSG, the intention was to avoid the potential for interference from multiple tasks. A major strength of the study is the sex balance (50% female with OSA), which is in contrast with the existing literature concerning sleep and overnight memory in OSA.

In summary, this study shows that in older adults, OSA can negatively impact sleep-dependent cognitive processing of a spatial navigation task, even when OSA is mild on average, without negatively impacting morning psychomotor vigilance. Slow wave activity appears to be an important marker of the brain's ability to process and utilize spatial information encountered during prior wakefulness, but whether and how OSA may impact slow wave sleep to influence memory are questions that can guide future work delineating the mechanistic links between OSA, SWA, forms of memory, and potential risk for cognitive decline in aging.

ABBREVIATIONS

AHI, apnea-hypopnea index
EEG, electroencephalography
NREM, non–rapid eye movement
OSA, obstructive sleep apnea
PSG, polysomnography
PVT, psychomotor vigilance testing
REM, rapid eye movement
SO, slow oscillation
SWA, slow wave activity
SWS, slow wave sleep

REFERENCES

1. Diekelmann S, Born J. The memory function of sleep. *Nat Rev Neurosci*. 2010; 11(2):114–126.
2. Ahuja S, Chen RK, Kam K, Pettibone WD, Osorio RS, Varga AW. Role of normal sleep and sleep apnea in human memory processing. *Nat Sci Sleep*. 2018;10: 255–269.
3. Stickgold R. Parsing the role of sleep in memory processing. *Curr Opin Neurobiol*. 2013;23(5):847–853.
4. Born J, Rasch B, Gais S. Sleep to remember. *Neurosci*. 2006;12(5):410–424.
5. Huber R, Ghilardi MF, Massimini M, Tononi G. Local sleep and learning. *Nature*. 2004;430(6995):78–81.
6. Kushida CA, Nichols DA, Holmes TH, et al. Effects of continuous positive airway pressure on neurocognitive function in obstructive sleep apnea patients: the Apnea Positive Pressure Long-term Efficacy Study (APPLES). *Sleep*. 2012;35(12): 1593–1602.
7. Osorio RS, Gumb T, Pirraglia E, et al; Alzheimer's Disease Neuroimaging Initiative. Sleep-disordered breathing advances cognitive decline in the elderly. *Neurology*. 2015;84(19):1964–1971.
8. Sharma RA, Varga AW, Bubu OM, et al. Obstructive sleep apnea severity affects amyloid burden in cognitively normal elderly: a longitudinal study. *Am J Respir Crit Care Med*. 2018;197(7):933–943.
9. Varga A, Wohlleber M, Giménez S, et al. reduced slow-wave sleep is associated with high cerebrospinal fluid Aβ42 levels in cognitively normal elderly. *Sleep*. 2016; 39(11):2041–2048.
10. Bubu OM, Andrade AG, Umasabor-Bubu OQ, et al. Obstructive sleep apnea, cognition and Alzheimer's disease: A systematic review integrating three decades of multidisciplinary research. *Sleep Med Rev*. 2020;50:101250.
11. Bubu OM, Pirraglia E, Andrade AG, et al. Alzheimer's Disease Neuroimaging Initiative. Obstructive sleep apnea and longitudinal Alzheimer's disease biomarker changes. *Sleep*. 2019;42(6):zsz048.

12. Cross N, Lampit A, Pye J, Grunstein RR, Marshall N, Naismith SL. Is obstructive sleep apnoea related to neuropsychological function in healthy older adults? A systematic review and meta-analysis. *Neuropsychol Rev*. 2017;27(4):389–402.
13. Kloepfer C, Riemann D, Nofzinger EA, et al. Memory before and after sleep in patients with moderate obstructive sleep apnea. *J Clin Sleep Med*. 2009;5(6):540–548.
14. Landry S, Anderson C, Andrewartha P, Sasse A, Conduit R. The impact of obstructive sleep apnea on motor skill acquisition and consolidation. *J Clin Sleep Med*. 2014;10(5):491–496.
15. Cellini N. Memory consolidation in sleep disorders. *Sleep Med Rev*. 2017;35: 101–112.
16. Djonlagic I, Saboisky J, Carusona A, Stickgold R, Malhotra A. Increased sleep fragmentation leads to impaired off-line consolidation of motor memories in humans. *PLoS One*. 2012;7(3):e34106.
17. Djonlagic I, Guo M, Matteis P, Carusona A, Stickgold R, Malhotra A. Untreated sleep-disordered breathing: links to aging-related decline in sleep-dependent memory consolidation. *PLoS One*. 2014;9(1):e85918.
18. Achermann P, Borbély AA. Low-frequency (< 1 Hz) oscillations in the human sleep electroencephalogram. *Neuroscience*. 1997;81(1):213–222.
19. Rasch B, Born J. About sleep's role in memory. *Physiol Rev*. 2013;93(2): 681–766.
20. Kim J, Gulati T, Ganguly K. Competing roles of slow oscillations and delta waves in memory consolidation vs forgetting. *Cell*. 2019;179(2):514–526.
21. Mander BA, Marks SM, Vogel JW, et al. β-amyloid disrupts human NREM slow waves and related hippocampus-dependent memory consolidation. *Nat Neurosci*. 2015;18(7):1051–1057.
22. Mander BA, Rao V, Lu B, et al. Prefrontal atrophy, disrupted NREM slow waves and impaired hippocampal-dependent memory in aging. *Nat Neurosci*. 2013;16(3): 357–364.
23. Ju YS, Ooms SJ, Sutphen C, et al. Slow wave sleep disruption increases cerebrospinal fluid amyloid-β levels. *Brain*. 2017;140(8):2104–2111.
24. Coughlan G, Laczó J, Hort J, Minihane AM, Hornberger M. Spatial navigation deficits - overlooked cognitive marker for preclinical Alzheimer disease? *Nat Rev Neurol*. 2018;14(8):496–506.
25 Coughlan G, Coutrot A, Khondoker M, Minihane A-M, Spiers H, Hornberger M. Toward personalized cognitive diagnostics of at-genetic-risk Alzheimer's disease. P*roc* N*atl* A*cad* S*ci*. 2019;116(19):9285–9292.
26. Wilson MA, McNaughton BL. Reactivation of hippocampal ensemble memories during sleep. *Science*. 1994;265(5172):676–679.
27. Girardeau G, Benchenane K, Wiener SI, Buzsáki G, Zugaro MB. Selective suppression of hippocampal ripples impairs spatial memory. *Nat Neurosci*. 2009; 12(10):1222–1223.
28. Skaggs WE, McNaughton BL. Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. *Science*. 1996;271(5257): 1870–1873.
29. Ferrara M, Iaria G, Tempesta D, et al. Sleep to find your way: the role of sleep in the consolidation of memory for navigation in humans. *Hippocampus*. 2008;18(8): 844–851.
30. Nguyen ND, Tucker MA, Stickgold R, Wamsley EJ. Overnight sleep enhances hippocampus-dependent aspects of spatial memory. *Sleep*. 2013;36(7):1051–1057.
31. Varga AW, Ducca EL, Kishi A, et al. Effects of aging on slow-wave sleep dynamics and human spatial navigational memory consolidation. *Neurobiol Aging*. 2016;42:142–149.
32. Varga AW, Kishi A, Mantua J, et al. Apnea-induced rapid eye movement sleep disruption impairs human spatial navigational memory. *J Neurosci*. 2014;34(44): 14571–14577.
33. Heinzer R, Vat S, Marques-Vidal P, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med*. 2015;3(4):310–318.
34. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991;14(6):540–545.
35. Dinges DF, Pack F, Williams K, et al. Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4-5 hours per night. *Sleep*. 1997;20(4):267–277.
36. Iber C, Ancoli-Israel S, Chesson AL Jr, Quan SF; for the American Academy of Sleep Medicine. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Specifications*. 1st ed. Westchester, IL: American Academy of Sleep Medicine; 2007.
37. Berry RB, Brooks R, Gamaldo CE, et al; for the American Academy of Sleep Medicine. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Specifications*. Version 2.0. Darien, IL: American Academy of Sleep Medicine; 2012.
38. Kishi A, Natelson BH, Togo F, Struzik ZR, Rapoport DM, Yamamoto Y. Sleep-stage dynamics in patients with chronic fatigue syndrome with or without fibromyalgia. *Sleep*. 2011;34(11):1551–1560.
39. Parekh A, Selesnick IW, Rapoport DM, Ayappa I. Detection of K-complexes and sleep spindles (DETOKS) using sparse optimization. *J Neurosci Methods*. 2015; 251:37–46.
40. Wickham H. *ggplot2: Elegant Graphics for Data Analysis*. New York: Springer; 2016.
41. Barner C, Ngo H-VV, Diekelmann S, Weeß H-G, Schlarb AA. Memory consolidation in fragmented sleep. *Somnologie (Berl)*. 2016;20(1):37–46.
42. Landry S, O'Driscoll DM, Hamilton GS, Conduit R. Overnight motor skill learning outcomes in obstructive sleep apnea: effect of continuous positive airway pressure. *J Clin Sleep Med*. 2016;12(5):681–688.
43. Djonlagic I, Guo M, Matteis P, Carusona A, Stickgold R, Malhotra A. First night of CPAP: impact on memory consolidation attention and subjective experience. *Sleep Med*. 2015;16(6):697–702.
44. Stickgold R, Walker MP. Memory consolidation and reconsolidation: what is the role of sleep? *Trends Neurosci*. 2005;28(8):408–415.
45. Kam K, Kang M, Eren CY, et al. Interactions between sleep disruption, motor learning, and p70 S6 kinase 1 signaling. *Sleep*. 2019;43(3):zsz244.
46. Tudor JC, Davis EJ, Peixoto L, et al. Sleep deprivation impairs memory by attenuating mTORC1-dependent protein synthesis. *Sci Signal*. 2016;9(425):ra41.
47. Boyce R, Glasgow SD, Williams S, Adamantidis A. Causal evidence for the role of REM sleep theta rhythm in contextual memory consolidation. *Science*. 2016; 352(6287):812–816.
48. Chen O, Castro-Alonso JC, Paas F, Sweller J. Extending cognitive load theory to incorporate working memory resource depletion: evidence from the spacing effect. *Educ Psychol Rev*. 2018;30(2):483–501.
49. Engle-Friedman M, Riela S, Golan R, et al. The effect of sleep loss on next day effort. *J Sleep Res*. 2003;12(2):113–124.
50. Iannella G, Vicini C, Colizza A, et al. Aging effect on sleepiness and apneas severity in patients with obstructive sleep apnea syndrome: a meta-analysis study. *Eur Arch Otorhinolaryngol*. 2019;276(12):3549–3556.
51. Peigneux P, Laureys S, Fuchs S, et al. Are spatial memories strengthened in the human hippocampus during slow wave sleep? *Neuron*. 2004;44(3):535–545.
52. Parekh A, Mullins AE, Kam K, Varga AW, Rapoport DM, Ayappa I. Slow-wave activity surrounding stage N2 K-complexes and daytime function measured by psychomotor vigilance test in obstructive sleep apnea. *Sleep*. 2019;42(3):zsy256.
53. Mullins AE, Kam K, Parekh A, Bubu OM, Osorio RS, Varga AW. Obstructive sleep apnea and its treatment in aging: effects on alzheimer's disease biomarkers, cognition, brain structure and neurophysiology. *Neurobiol Dis*. 2020;145:105054.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication August 25, 2020
Submitted in final revised form December 14, 2020
Accepted for publication December 14, 2020
Address correspondence to: Andrew W. Varga, MD, PhD, and Anna E. Mullins, RPSGT, PhD, One Gustave L. Levy Place, Annenberg 21-44, New York, NY 10029; Email: andrew.varga@mssm.edu and anna.mullins@mssm.edu

DISCLOSURE STATEMENT

All authors have read and approved the final manuscript. Work for this study was performed at the authors' respective institutions. This work was supported by grants from NIH/NIA/NHLBI R01AG056682, R21AG059179, R21AG055002, R01HL118624, R01AG022374, R01AG056531, R01AG056031, K24 HL109156, and P30AG008051; Alzheimer's Association grant 2018-AARG-589632; Merck Investigator Studies Program; the American Sleep Medicine Foundation Junior Faculty Award 152-JF-16; the American Thoracic Society Foundation; and the Friedman Brain Institute. The authors report no conflicts of interest.