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The Effect of Obstructive Sleep Apnea on Sleep-dependent Emotional Memory Consolidation

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Abstract

Rationale: A growing body of evidence suggests that sleep is critical for the adaptive processing and consolidation of emotional information into long-term memory. Previous research has indicated that emotional components of scenes particularly benefit from sleep in healthy groups, yet sleep-dependent emotional memory processes remain unexplored in clinical cohorts, including those with obstructive sleep apnea (OSA). This line of research is important as it will add to the understanding of how disrupted sleep in OSA contributes to both impaired cognition and emotion dysregulation.

Objectives: To test the hypothesis that individuals with OSA will have impaired sleep-dependent memory consolidation, with the greatest impact being on memory for emotional content.

Methods: In this study, a group of newly diagnosed patients with OSA ($n = 26$; 10 female; average age, 42.5 years) and a matched group of healthy control subjects ($n = 24$; 13 female; average age, 37 years) were enrolled in the study at Beth Israel Deaconess Medical Center. Participants encoded scenes with negative or neutral foreground objects placed on neutral backgrounds before a night of polysomnographically recorded sleep. In the morning, they completed a recognition test in which old and new scene objects and backgrounds, presented separately and one at a time, were judged as old, new, or similar compared with what had been previously viewed.

Results: Patients with OSA had a deficit in recognition memory for the scenes. Overall recognition (the ability to recognize old items as either old or similar) was impaired across all scene elements, both negative and neutral objects and backgrounds, whereas specific recognition (correctly identifying old items as old) was impaired only for negative objects. Across all participants, successful overall recognition correlated positively with sleep efficiency and rapid eye movement (REM) sleep, whereas successful specific memory recognition correlated only with REM sleep.

Conclusions: Our findings indicate that fragmented sleep and reduced REM sleep, both hallmarks of OSA, are associated with disruptions in general memory impairment and veridical memory for emotional content, which could alter emotional regulation and contribute to comorbid emotional distress in OSA.

Keywords: emotional memory; obstructive sleep apnea; rapid eye movement sleep; sleep efficiency; sleep-dependent memory consolidation

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This article has a related editorial.

This article has a data supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

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Advances in neuroscience have increased our understanding of the multifaceted relationships between memory systems and sleep, whereby sleep has become increasingly recognized as a favorable state for brain plasticity and memory consolidation (1–3). Although sleep is associated with benefits for multiple forms of declarative memory (4), evidence suggests sleep plays a particularly active role in the modulation and consolidation of emotional memories (5). Specifically, rapid eye movement (REM) sleep has been shown to predict the successful consolidation of negative information (6–8). Moreover, sleep has been shown to have the ability to prioritize aspects of memory, stabilizing and enhancing content deemed important (e.g., emotional elements), whereas information that is less important or useful (e.g., neutral peripheral details) is attenuated (9–11).

Although undisturbed sleep promotes this type of memory consolidation, insufficient and interrupted sleep can result in memory impairment (12–14). Obstructive sleep apnea (OSA) is a common sleep disorder associated with sleep disruption and intermittent hypoxia in at least 6–13% of middle-aged individuals in the United States and up to 1 billion people worldwide (15, 16). Previous research examining patients with OSA using traditional single-session neurocognitive tests has demonstrated various areas of cognitive deficits but, at times, has failed to produce consistent findings (17–22). Because of the complexity of the human memory system and these inconsistent and sometimes contradictory results, the precise memory systems affected by OSA require clarification.

Although research to date has implicated OSA in impairments of overnight motor, spatial, and declarative memory consolidation (23–26), given the high prevalence of depressive (35%) and anxious (32%) symptoms in patients with OSA (27), it is surprising that, to our knowledge, there have been no rigorous studies focusing on the effect of OSA on sleep-dependent emotional memory consolidation. An investigation into the effects of OSA on emotional memory is especially warranted, given that OSA can be particularly disruptive to REM sleep continuity as decreased genioglossus muscle tone leads to increased upper airway collapse during this sleep stage (28).

Given the extensive sleep disruption, cognitive deficits, and high prevalence of psychopathology in patients with OSA, we examined the impact of OSA on the consolidation of emotional and neutral aspects of memory across a night of sleep. Taking into account research demonstrating that sleep, and REM sleep, in particular, bolsters the consolidation of negative aspects of memory over neutral elements (7–10), we hypothesized that OSA would be associated with a distinct impairment in memory for negative content. The emotional tradeoff (ETO) task used here is particularly well-suited to make this distinction as it not only assesses changes in memory for negative versus neutral elements of complex scenes, but also allows for the direct comparison of memory for negative content (i.e., negative objects) between groups. Furthermore, we predicted that the impairment in memory for negative information would be associated with measures of decreased sleep continuity, increased OSA symptomatology (e.g., apnea–hypopnea index [AHI]), and reduced REM sleep.This work has been previously presented virtually as part of the Harvard Medical School Division of Sleep Medicine's Annual Sleep and Health Benefit Day (October 2020) and at the 35th annual meeting of the APSS (Associated Professional Sleep Societies) SLEEP meeting (July 2021).

Study Design and Methods

A total of 52 participants ($n = 26$ patients with newly diagnosed OSA, $n = 26$ healthy control participants) were included in this case-control study. Participants were screened for the study at BIDMC (Beth Israel Deaconess Medical Center). They were recruited from the greater Boston area through flyers and advertisements and from local sleep clinics. The diagnosis of OSA was defined by an AHI greater than 5 per hour. Patients with OSA were newly diagnosed with no prior exposure to continuous positive air pressure. In addition, potential

Table 1. Demographics

	Control Participants, $n = 24$	Patients with OSA, $n = 26$
Female sex, *n* (%)	13 (54.2)	10 (40.0)
APOE ε4-positive, *n* (%)	8 (33)	7 (27)
Race, *n* (%)		
Asian	2 (8.3)	2 (7.7)
Black	3 (12.5)	3 (11.5)
Native Hawaiian or other Pacific Islander	0 (0)	0 (0)
American Indian or Alaska Native	0 (0)	0 (0)
>1 race	1 (4.2)	0 (0)
White	16 (66.7)	18 (69.2)
Unknown or not reported	2 (8.3)	3 (11.5)
Ethnicity, *n* (%)		
Hispanic	2 (8.3)	5 (19.2)
Not Hispanic	16 (66.7)	16 (61.5)
Unknown or not reported	6 (25)	5 (19.2)
	Control Participants $n = 24$ (M ± SE)	**Patients with OSA $n = 26$ (M ± SE)**
Age, yr	37.0 ± 2.6	42.5 ± 2.4
BMI, kg/m^2	25.7 ± 0.9	29.3 ± 1.3
BDI-II	4.9 ± 1.5	4.6 ± 1.0
WASI full scale	182.8 ± 10.3	191.8 ± 8.8
WASI percentile	55.9 ± 5.3	51.6 ± 9.4
Morningness–eveningness scale (44)	20.6 ± 1.0	19.7 ± 0.8
Epworth sleepiness scale (45)	5.7 ± 0.9	6.4 ± 0.6
Stanford sleepiness scale PM	2.8 ± 0.3	2.6 ± 0.2
Stanford sleepiness scale AM	3.0 ± 0.3	2.9 ± 0.3

Definition of abbreviations: APOE ε4 = genetic variant of the apolipoprotein E gene on chromosome 19; BDI-II = Beck Depression Inventory II; BMI = body mass index; M = mean; OSA = obstructive sleep apnea; SE = standard error; WASI = Wechsler Abbreviated Scale Intelligence.
See Table E4 for inclusion of test statistics and *P* values (chi-square statistics used for comparison of categorical metrics; Kruskal-Wallis *H* test conducted on continuous variables).

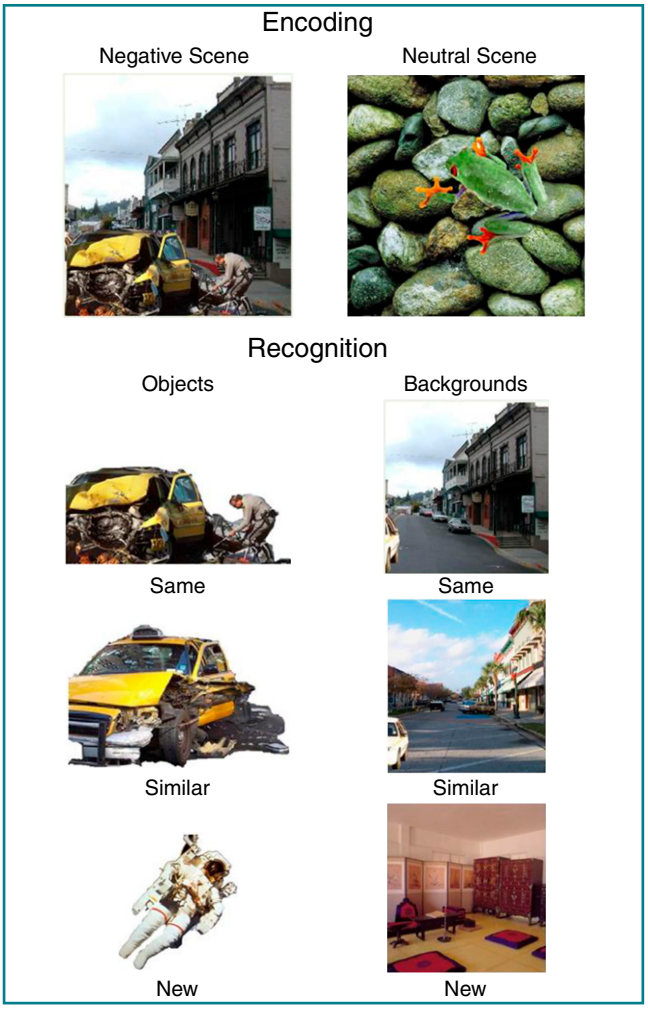

Figure 1. Sample stimuli used during the encoding and recognition sessions of the emotional memory tradeoff paradigm.

healthy control participants with no subjective sleep complaints underwent a standard baseline overnight polysomnography (PSG) sleep recording, which served both as an adaptation to the overnight testing conditions and to permit diagnosis of any previously undetected sleep disorders.

Eligibility criteria included age between 18 and 70 years (range, 22–70 years; mean, 39.9 years; SD, 12.6); good health as determined by reported medical and psychiatric history and a physical examination; absence of any medical or psychiatric disorders (other than OSA and treated hypertension) that could influence excessive daytime sleepiness; the ability to maintain a regular sleep schedule, complete self-rating scales, and participate in computer-based testing; as well as an agreement to abstain from alcohol consumption from the day before the study through the end of the study. Participants with a periodic limb movement index greater than 15 per hour (control: $n = 1$) were excluded. One control participant was excluded from the analysis because of technical difficulties, leaving a total of $n = 50$ ($n = 26$ patients with OSA, $n = 24$ control participants) in the final analysis. All participants provided informed written consent, and the study procedures were approved by the partners' and BIDMC's institutional review boards.

Study Procedures

During the initial clinical screening visit, all participants completed a battery of clinical assessments reported in Table 1. On the night of their study visit, participants arrived at 21:00 and completed the Stanford Sleepiness Scale (29) and a 5-minute version of the psychomotor vigilance task, a measure of sustained attention and reaction time (30). They then completed the encoding session of the emotional memory tradeoff task (31) (*see* below) before retiring for a night of PSG-recorded sleep. From this sleep period, scored hypopneas required a peak signal excursion drop by 30% or higher of baseline before the event using nasal pressure, associated with either an oxygen desaturation of greater than 3% or arousal lasting 10 seconds or less (*see* the data supplement for additional PSG and sleep scoring protocol).

In the morning, participants were awoken and immediately asked to complete a dream mentation report followed by a reassessment of the Stanford Sleepiness Scale and psychomotor vigilance task. They then completed the recognition session of the ETO, as described below. Finally, all participants went through a venous blood draw to determine their APOE (apolipoprotein E) genotype.

ETO

Participants completed the ETO (31), a task of emotional learning that has been repeatedly validated as an assessment of sleep-dependent emotional memory consolidation (7, 9–11, 32, 33). During the evening encoding session, participants were asked to study 64 scenes, 32 with neutral objects (e.g., a chipmunk) on neutral backgrounds and 32 with negatively arousing objects (e.g., a scary spider), also on neutral backgrounds. The emotionality of each scene component had been validated in a previous study (31), and participants were shown one of four different sets of images to control for potential list effects (19, 20). Each scene was displayed for 5 seconds on a computer screen, and once removed, participants were asked to indicate whether they would approach or move away from the scene (1 = definitely move closer and 7 = definitely move away).

In the morning, participants performed a self-paced recognition task in which they were presented with objects and backgrounds separately and one at a time, in random order. Each item in the recognition task had either been studied previously (same; e.g., the same scary spider seen at encoding), was similar, but not identical, to a studied item (similar; e.g., a different scary spider), or was entirely new (new; e.g., a dog). The recognition task included 32 same objects (16 negative

Table 2. Comparison of nocturnal polysomnography sleep data between patients with obstructive sleep apnea and healthy control participants

	Patients with OSA $n = 26$ (M ± SE)	Control Participants $n = 24$ (M ± SE)	Mean Difference	95% CI Lower	95% CI Upper	Kruskal-Wallis *H*	*P* Value
TST, min	405.3 ± 8.7	442.7 ± 14.7	−37.44	−71.21	−3.66	4.61	0.03
Sleep efficiency, %	80.1 ± 2.0	87.14 ± 1.8	−7.06	−12.49	−1.64	8.04	0.01
Awakenings, n	14.3 ± 1.3	12.0 ± 1.3	2.23	1.86	−1.50	1.28	0.26
WASO, min	105.7 ± 12.9	65.0 ± 9.4	40.68	8.19	73.17	7.50	0.01
N1, %	4.8 ± 1.0	2.3 ± 0.5	2.49	0.38	4.60	3.44	0.06
N1, min	19.3 ± 3.7	9.3 ± 1.6	10.01	1.62	18.42	2.83	0.09
N2, %	70.8 ± 2.35	63.8 ± 2.0	7.01	0.76	13.26	5.07	0.02
N2, min	285.9 ± 10.2	278.7 ± 8.8	7.2	−20.04	34.46	0.06	0.81
SWS, %	6.6 ± 1.2	9.6 ± 1.6	−2.93	−6.84	0.98	2.10	0.15
SWS, min	27.2 ± 4.8	45.1 ± 8.0	−17.91	−36.26	0.44	2.67	0.10
REM, %	17.8 ± 1.8	24.3 ± 1.3	−6.57	−11.07	−2.07	7.60	0.01
REM, min	72.8 ± 7.6	109.6 ± 7.7	−36.76	−58.54	−14.97	8.83	0.003
Arousal index, events/h	27.5 ± 4.1	20.0 ± 1.6	7.54	−1.63	16.72	1.55	0.21
AHI, events/h	23.5 ± 5.0	2.1 ± 0.3	21.41	10.92	31.91	36.72	<0.001
REM-AHI, events/h	18.7 ± 4.9	4.2 ± 0.8	14.49	4.16	24.83	11.10	0.001
Mean oxygen saturation, %	94.6 ± 0.4	96.3 ± 0.3	−1.74	−2.85	−0.63	12.94	<0.001
Oxygen nadir, %	86.3 ± 1.4	92.7 ± 0.6	−6.40	−9.58	−3.22	17.98	<0.001
PLM index, events/h	0.09 ± 0.05	0.01 ± 0.01	0.08	−0.03	0.19	0.74	0.39

Definition of abbreviations: AHI = apnea–hypopnea index; CI = confidence interval; M = mean; N1 = stage 1 sleep; N1 (%) = percentage of sleep period spent in stage 1 sleep; N2 = stage 2 sleep; N2 (%) = percentage of sleep period spent in stage 2 sleep; OSA = obstructive sleep apnea; PLM = periodic limb movement; REM = rapid eye movement; REM (%) = percentage of sleep period spent in REM sleep; REM-AHI = apnea–hypopnea index during REM sleep; SE = standard error; SWS = slow wave sleep; SWS (%) = percentage of sleep period spent in slow wave sleep; TST = total sleep time; WASO = wake after sleep onset.
Comparison between groups done using Kruskal Wallis *H* test.

arousing and 16 neutral), 32 similar objects (16 negative arousing and 16 neutral), 32 new objects (16 negative arousing and 16 neutral), 32 same backgrounds (16 previously shown with a negative arousing object and 16 shown with a neutral object), 32 similar backgrounds (similar to 16 previously shown with a negative arousing object and 16 similar to backgrounds shown with a neutral object), and 32 new backgrounds (*see* Figure 1). Participants were asked to identify each object and background presented as same, similar, or new. For each studied object, either the identical object or a similar one was presented, but not both.

Statistical Analysis

For the ETO task, memory retention of the objects was calculated separately for each valence (negative and neutral) and scene component (objects and backgrounds). The magnitude of the object–background tradeoff was calculated as the difference between object and background memory

Table 3. Analysis of variance results for overall recognition memory

	$F_{1,48}$	*P* Value	η_p^2	*Post Hocs*	*t* and *F*	*P* Value	*d*
Group	13.5	0.001*	0.22	Significant for each component × valence (*see* Table 5)	$F > 6.4$ for all	≤0.015*	—
Scene component	57.7	<0.001*	0.55	Objects remembered significantly better than backgrounds	$t(49) = 7.58$	<0.001*	1.07
Valence	0.95	0.34	0.02	N/A	—	—	—
Group × scene component	0.81	0.37	0.02	N/A	—	—	—
Group × valence	0.15	0.70	0.003	N/A	—	—	—
Scene component × valence	102.9	<0.001*	0.68	Neg: objects better than backgrounds	OSA: $t(25) = 7.2$ CTRL: $t(23) = 8.6$	<0.001* <0.001*	1.40 1.72
				Neutral: no significant differences	OSA: $t(25) = 0.53$ CTRL: $t(23) = 1.66$	0.60 0.11	— —
Group × scene component × valence	0.6	0.45	0.01	N/A	—	—	—

Definition of abbreviations: CTRL = healthy control participants; $F_{1,48}$ = ANOVA *F*-value with the degrees of freedom for this sample; N/A = not applicable; OSA = patients with obstructive sleep apnea; η_p^2 = partial eta squared effect size.
*Significance set at $P \leq 0.05$.

Table 4. Analysis of variance results for specific recognition memory

	$F_{1,48}$	*P* Value	η_p^2	*Post Hocs*	*t* and *F*	*P* Value	*d*
Group	3.0	0.09	0.06	Significant only for negative objects (*see* Table 5)	—	—	—
Scene component	110.8	<0.001*	0.61	Objects remembered significantly better than backgrounds	$t(49) = 7.82$	<0.001*	1.10
Valence	0.94	0.34	0.02	N/A	—	—	—
Group × scene component	2.36	0.13	0.05	N/A	—	—	—
Group × valence	0.63	0.43	0.01	N/A	—	—	—
Scene component × valence	70.0	<0.001*	0.49	Neg: objects better than backgrounds	OSA: $t(25) = 6.1$ CTRL: $t(23) = 11.2$	OSA: <0.001* CTRL: <0.001*	1.19 2.34
				Neutral: no significant differences	OSA: $t(25) = 0.48$ CTRL: $t(23) = 0.99$	0.64 0.33	— —
Group × scene component × valence	0.07	0.79	0.002	N/A	—	—	—

Definition of abbreviations: CTRL = healthy control participants; $F_{1,48}$ = ANOVA *F*-value with the degrees of freedom for this sample; N/A = not applicable; OSA = patients with obstructive sleep apnea; η_p^2 = partial eta squared effect size.
*Significance set at $P \leq 0.05$.

scores within the same valence (e.g., negative tradeoff = memory for negative objects minus memory for their backgrounds).

To investigate OSA effects on memory specificity, we calculated both overall and specific memory recognition scores. Consistent with previous research (9, 34), a lenient overall recognition score was calculated by computing the proportion of both same and similar responses to same items, as this combined score reflects memory for at least some aspect of the studied items (e.g., saying "similar" to spider they previously viewed). The more conservative specific recognition score (i.e., counting only same responses to same items) was computed to capture veridical memory for the precise visual details of a studied item. To correct for response bias, we calculated corrected memory scores by subtracting the proportion of false alarms (i.e., same judgments to new pictures) of each object type from the proportion of hits (35). Analysis of general or gist memory (9, 31) (a third previously reported memory calculation used with the ETO task) is presented in the data supplement.

Memory, demographic (Table 1), and sleep variables (Table 2) were compared between control participants and patients with OSA. Pearson's chi-squared tests and Kruskal-Wallis *H* tests were performed to compare demographic and PSG-derived sleep data. The initial memory analysis used repeated measures analysis of variance (ANOVA) and follow-up *t* tests with relevant effect sizes reported (Tables 3 and 4), as is standard when analyzing the ETO task (9, 10, 31, 34) to confirm the existence of the tradeoff effect and to potentially identify the group (OSA vs. control) by scene component type (object vs. background) by valence (negative vs. neutral) interactions. These initial analyses were followed up by between-group Kruskal-Wallis *H* tests and within-group Wilcoxon rank-sum tests for all relevant memory calculation outcomes. Mean difference and 95% confidence intervals were reported for all group comparisons of PSG and memory measures.

We also conducted regression analyses between *a priori*-selected sleep and memory variables. For these analyses, we calculated total scores for overall and specific memory by averaging memory scores across all scene component and valence categories. This approach was used to reduce comparisons and determine the impact of OSA on memory as a whole. In addition, in line with previous research that suggests that emotional memory consolidation is benefited by sleep, particularly REM sleep (6–8, 36), our *a priori* prediction was that negative object memory would be associated positively with categorical metrics of sleep efficiency (wake after sleep onset [WASO]), negatively with OSA-related symptoms (AHI and REM-related AHI) and positively with REM sleep amount (REM sleep time and percent of time spent in REM sleep [REM%]) (7). As each of the metrics within each category are themselves highly correlated (sleep efficiency: $r[50] = -0.98$, $P < 0.001$; OSA-related symptoms: $r[50] = 0.87$, $P < 0.001$; REM sleep: $r[50] = 0.95$, $P < 0.001$), we only Bonferroni-corrected for the three categories of analysis, setting $P = 0.017$ for significant findings. Given the novelty of this study, we then performed exploratory correlations with all outcome measures of sleep and memory. These results are presented in the data supplement to assist future researchers with meta-analyses and hypothesis generation.

Results

Demographic variables are reported in Table 1, and there were no notable differences between control participants and patients with OSA (*see* Table E4 in the data supplement for inclusion of test statistics and *P* values). There were no group differences in any metric of vigilance during the evening or morning testing sessions. There were also no group differences in dream reports, and dream reports had no relationship with memory performance (*see* the data supplement for additional details).

Group comparison of sleep data with 95% confidence intervals is presented in Table 2. Control participants had more total sleep times and higher sleep efficiencies. Patients with OSA experienced more WASO, spent more time and percent of sleep in stage one, and had a higher percentage of stage two sleep but spent less time and a smaller proportion of their sleep in REM. The time and percent of sleep spent in slow-wave sleep were similar between groups.

As expected, the mean AHI was greater for patients (23.5/h ± 5.0) than for control participants (2.1/h ± 0.3). Similarly, mean

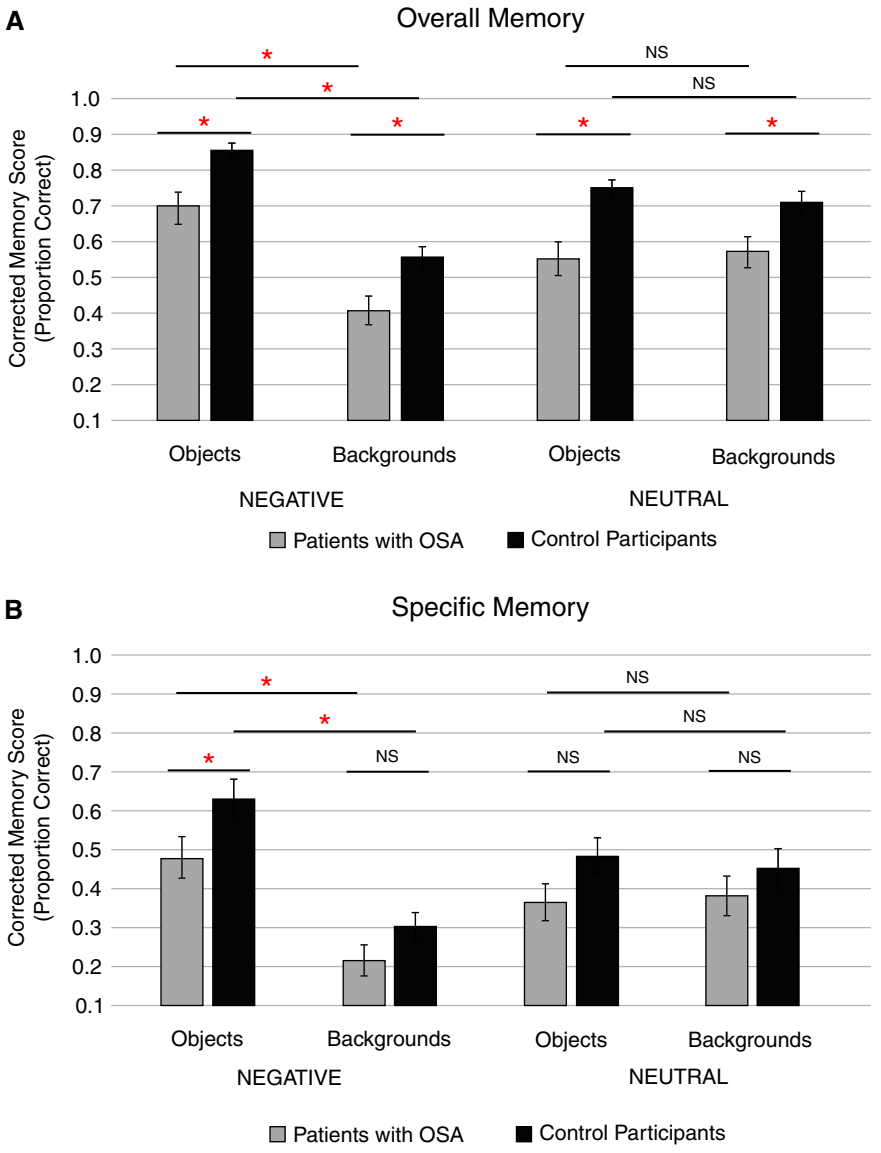

Figure 2. Memory results for overall and specific memory scores. (*A*) Patients with obstructive sleep apnea (OSA) had significant impairments in all aspects of corrected overall recognition memory (hits [same or similar responses to same images] − false alarms) in the emotional memory tradeoff task, regardless of component or valence. Despite this impairment, the pattern of the emotional memory tradeoff is preserved in patients with OSA. (*B*) When memory for the emotional memory tradeoff task is calculated using the more conservative corrected specific recognition memory (hits [only same responses to same images] − false alarms), the pattern of the emotional memory tradeoff is again preserved in both patients with OSA and healthy control participants. Patients with OSA, however, demonstrate a distinct and significant impairment in specific memory for negative central objects. *$P \leq 0.05$ on the basis of Kruskal-Wallis *H* tests. NS = not significant.

oxygen saturation and oxygen nadir were lower in patients. No group differences were seen for the arousal index, the number of awakenings, or periodic limb movements.

Overall Recognition Memory

We first compared the groups on the more lenient overall memory score (responding "same" or "similar" to same items) for the separately presented objects and backgrounds of the negative and neutral scenes. To determine if there was an interaction, we ran a 2 (group: OSA or control) × 2 (scene component: object or background) × 2 (object valence: negative or neutral) ANOVA, with scene component and valence as repeated measures (31) (Table 3).

This analysis revealed a main effect of group (OSA vs. control), with follow-up Kruskal-Wallis *H* tests revealing an impairment of memory in the OSA group across all scene components and valences (Figure 2A and Table 5). There was also a main effect of the scene component (objects vs. backgrounds) and a two-way interaction between the scene component and valence (negative or neutral). *Post hoc* analyses revealed that memory for negative objects was better than memory for their paired backgrounds in both groups ($d \geq 1.40$ indicating large effects), whereas there was no difference in overall recognition memory between neutral objects and their backgrounds in either group. The three-way interaction was not significant, and there was no main effect of valence or a two-way interaction between the group and either scene component or valence.

Critically, Wilcoxon rank-sum tests indicated that the object–background difference in memory was greater for negative than neutral scene components in both groups (Table 6), confirming that, despite the global impairment in overall memory, the emotional tradeoff effect was preserved in the OSA group.

Finally, we correlated total and negative object overall memory scores with sleep efficiency, WASO, AHI, REM-related AHI, REM time, and REM% (Table 7). For both total memory and negative object memory, we found a positive correlation with sleep efficiency (Figure 3, top) and a significant negative correlation with WASO. Furthermore, there was a positive correlation between total overall memory and minutes in REM sleep. The association with REM% failed to reach significance after corrections for multiple comparisons (Table 7). No correlations remained significant when run separately for each group (all $P > 0.06$), and Fisher–*z* comparisons between OSA and control group correlations were nonsignificant (all $P \geq 0.55$).

Specific Memory Group Comparison

We next examined the impact of OSA on the stricter measure of memory performance, specific memory (i.e., only including responses of same to same items) (Table 4). Starting again with a repeated measures ANOVA to test for interactions, there was a significant main effect of scene component (objects vs. backgrounds) and a scene

Table 5. Between-group corrected memory comparisons

	Control Participants $n = 24$ (M ± SE)	Patients with OSA $n = 26$ (M ± SE)	Mean Difference	95% CI Lower	95% CI Upper	Kruskal-Wallis *H*	*P* Value
Corrected Overall Recognition Memory							
Negative objects	0.85 ± 0.04	0.69 ± 0.04	0.16	0.05	0.26	6.93	0.008*
Backgrounds paired with negative objects	0.55 ± 0.04	0.41 ± 0.04	0.15	0.04	0.25	8.86	0.003*
Magnitude of negative object–background tradeoff	0.30 ± 0.04	0.29 ± 0.04	0.01	−0.09	0.12	<0.001	0.99
Neutral objects	0.75 ± 0.04	0.55 ± 0.04	0.20	0.09	0.30	9.86	0.002*
Backgrounds paired with neutral objects	0.71 ± 0.04	0.57 ± 0.04	0.14	0.03	0.25	5.05	0.03*
Magnitude of neutral object–background tradeoff	0.04 ± 0.03	−0.02 ± 0.04	0.06	−0.03	0.14	2.55	0.11
Corrected Specific Recognition Memory							
Negative objects	0.63 ± 0.06	0.48 ± 0.05	0.15	<0.001	0.31	4.66	0.03*
Backgrounds paired with negative objects	0.30 ± 0.04	0.22 ± 0.04	0.09	−0.03	0.20	3.29	0.07
Magnitude of negative object–background tradeoff	0.33 ± 0.03	0.26 ± 0.04	0.07	−0.04	0.17	1.81	0.18
Neutral objects	0.48 ± 0.05	0.36 ± 0.05	0.12	−0.02	0.26	3.27	0.07
Backgrounds paired with neutral objects	0.45 ± 0.05	0.38 ± 0.05	0.07	−0.08	0.22	0.98	0.32
Magnitude of neutral object–background tradeoff	0.03 ± 0.03	−0.02 ± 0.04	0.05	−0.05	0.15	1.40	0.24

Definition of abbreviations: CI = confidence interval; M = mean; OSA = obstructive sleep apnea; SE = standard error.
Between-group (obstructive sleep apnea patients versus healthy control participants) comparisons of corrected overall (top) and specific (bottom) memory scores for each valence and scene type and between-group comparisons of the magnitude of the object–background differences for each valence. Comparison between groups done using the Kruskal-Wallis *H* test.
*Significance set at $P \leq 0.05$.

component × valence (negative vs. neutral) interaction. In both groups, specific memory for negative objects was significantly better than memory for their backgrounds ($d \geq 1.19$ indicating large effects), whereas the difference between neutral objects and their paired backgrounds was nonsignificant in both groups (Table 4). Furthermore, Wilcoxon rank-sum tests indicated that the object–background difference in memory was again greater for negative compared with neutral scenes in both groups (Table 6), confirming the ETO effect for specific memory in both groups. The ANOVA with this stricter measure of memory revealed no main effect of group or three-way group × scene component × valence interaction. However, given our *a priori* prediction that OSA would have a larger impact on memory for negative material, we conducted Kruskal-Wallis *H* tests separately on each valence and scene component type. Unlike overall memory, for which all elements and valences of memories were significantly poorer in patients with OSA, specific memory analyses revealed significant impairment only for negative objects (Figure 2B and Table 5). Specific memory for all other scene components and valence types were statistically similar between groups.

We then correlated total and negative object-specific memory scores with the same sleep measures used for overall memory (Table 7). Total specific memory correlated positively with REM% and REM time (Figure 3, bottom). We also found relationships between specific negative object memory and sleep efficiency, REM%, and REM time (Table 7), but these associations did not persist after correction for multiple comparisons. No correlations remained significant when run separately for each group (all $P > 0.09$), and Fisher–*z* comparisons between OSA and control group correlations were nonsignificant (all $P \geq 0.89$). Additional exploratory correlations can be found in the data supplement.

Discussion

To our knowledge, this is the first study to explore the impact of OSA on sleep-dependent consolidation of complex emotional and neutral memories. Results using a well-validated sleep-dependent emotional memory paradigm (9–11) indicate that, when using a more lenient measure of overall memory, patients with OSA exhibit significant impairments after sleep for all memory components, regardless of valence or scene component type, indicating severe cognitive consequences of OSA. Using the stricter measure of a specific memory, however, we found reduced performance exclusively for negative emotional objects. This finding suggests that when memory is measured for veridical recognition, patients with OSA demonstrate a distinct and significant overnight deterioration in emotional aspects of memory.

One intriguing finding is that despite the OSA-driven deficits in both specific and overall memory, the pattern of the ETO effect was preserved in OSA. In both control participants and patients with OSA, memory for negative objects after sleep was significantly greater than for their paired backgrounds, whereas memory for neutral objects and their backgrounds was equivalent. Furthermore, the magnitude of the ETO was significant in both groups, regardless of memory score calculation.

Table 6. Within-group object–background tradeoff comparisons

	Within-group Object–Background Tradeoff Comparisons						
	Negative Tradeoff (M ± SE)	Neutral Tradeoff (M ± SE)	Mean Difference	95% CI Lower	95% CI Upper	Wilcoxon Z	*P* Value
Healthy control participants							
Overall negative–neutral tradeoff comparison	0.30 ± 0.04	0.04 ± 0.02	0.26	0.19	0.34	4.05	<0.001
Specific negative–neutral tradeoff comparison	0.33 ± 0.03	0.03 ± 0.03	0.30	0.21	0.39	3.93	<0.001
Patients with OSA							
Overall negative–neutral tradeoff comparison	0.29 ± 0.04	−0.02 ± 0.04	0.22	0.22	0.39	4.23	<0.001
Specific negative–neutral tradeoff comparison	0.26 ± 0.04	−0.02 ± 0.04	0.28	0.18	0.38	3.94	<0.001

Definition of abbreviations: CI = confidence interval; M = mean; OSA = obstructive sleep apnea; SE = standard error.
Within-group comparison of overall and specific object–background tradeoff scores between negative and neutral scenes within healthy control participants (top) and patients with obstructive sleep apnea (bottom). Both groups show substantially greater negative compared with neutral memory tradeoffs. Within-group comparisons were made using Wilcoxon signed-rank *Z* test. Values reported here are tradeoff scores, or the difference in the proportion of correct responses between objects and backgrounds for each type of central stimulus valence (negative and neutral). The Mean Difference Score is thus the difference between the Negative Tradeoff and Neutral Tradeoff.

Although the ETO effect has previously been shown to be relatively stable across aging (33, 37), this finding suggests that the robust memory systems designed to prioritize emotional memory during sleep also withstand the deleterious effects of OSA during the consolidation period.

When exploring the relationships between memory and sleep architecture, we found that across all participants, total specific memory correlated positively with measures of REM sleep. On the basis of previous reports (7, 38), we had anticipated these findings, but, as indicated in the data supplement, exploratory analyses found that REM sleep was associated with the most emotional memory tradeoff components when calculated using specific memory, indicating that REM sleep might have a much broader effect on this memory type (*see* Table E1). These findings may have particular implications for REM-predominant OSA, especially given that a high REM AHI is often ignored clinically in the presence of an overall AHI under 5 per hour.

Total and negative object overall memory performance correlated positively with sleep efficiency and negatively with WASO. This finding suggests that the quality and continuity of sleep may be particularly important for overall memory consolidation. However, as described in the data supplement, this was true for the overall memory of all scene components and valence types (*see* Table E1). Thus, the relationship between sleep quality and continuity seems to be related to the consolidation of memory traces in general, not specific to a particular valence.

Although OSA results in both sleep fragmentation and hypoxemia, we found no association between emotional memory consolidation and hypoxia, similar to animal research demonstrating the importance of sleep continuity independent of intermittent hypoxia (39, 40). Furthermore, we have previously demonstrated that increased sleep fragmentation in patients with OSA impairs motor memory consolidation in the absence of significant hypoxemia (41). We also observed in a previous study examining the effect of OSA on declarative memory that it was the impact of OSA on sleep architecture (in this case, the amount of non-REM slow wave sleep (N3)) rather than the sleep fragmentation that caused the deficit in memory impairment (42). Together, these studies would argue that memory impairment is a function of the individual's brain processing of OSA reflected by changes in sleep architecture rather than the fragmentation itself.

Our results extend the literature demonstrating the negative impact of OSA on offline memory processing, a literature that has largely focused on motor, spatial, and declarative memory consolidation (23–26). Further research in OSA cohorts will be needed to understand better the relationship between sleep structure and emotional memory processing, especially as related to electroencephalogram spectral power and sleep spindles.

Strengths and Limitations

A particular strength of this report is the demographic similarities of the two groups, matched for age, sex, APOE ε4 prevalence, race, ethnicity, intelligence, body mass index, and morningness–eveningness (*see* Table 1). All clinical measures assessed and alertness measures were similar between groups on the basis of 95% confidence intervals. Importantly, self-reported depression was equivalent between groups and, overall, very low (average Beck Depression Inventory less than 5). As a consequence, we can, with good confidence, attribute the observed differences in memory performance to the effects of OSA on sleep.

At the same time, the low degree of depressive symptoms reported by the patients with OSA is a notable limitation of the study. Although the similarity between groups is beneficial in demonstrating that these memory effects are specifically associated with OSA-related sleep disruption and not with comorbid depression in OSA, there is extensive research indicating that patients with OSA typically experience higher degrees of depression compared with non-OSA (43). Moreover, whereas OSA symptomatology differed substantially between the groups, the severity of our OSA sample averaged out to the moderate range of OSA severity (average, 23.5 events per hour). The associations reported in both Table 7 and the exploratory analyses in the data supplement provide some evidence that ETO performance may be related to the degree of OSA severity, and it is possible that severe OSA may generate different changes in negative memory and tradeoff performance compared with mild to

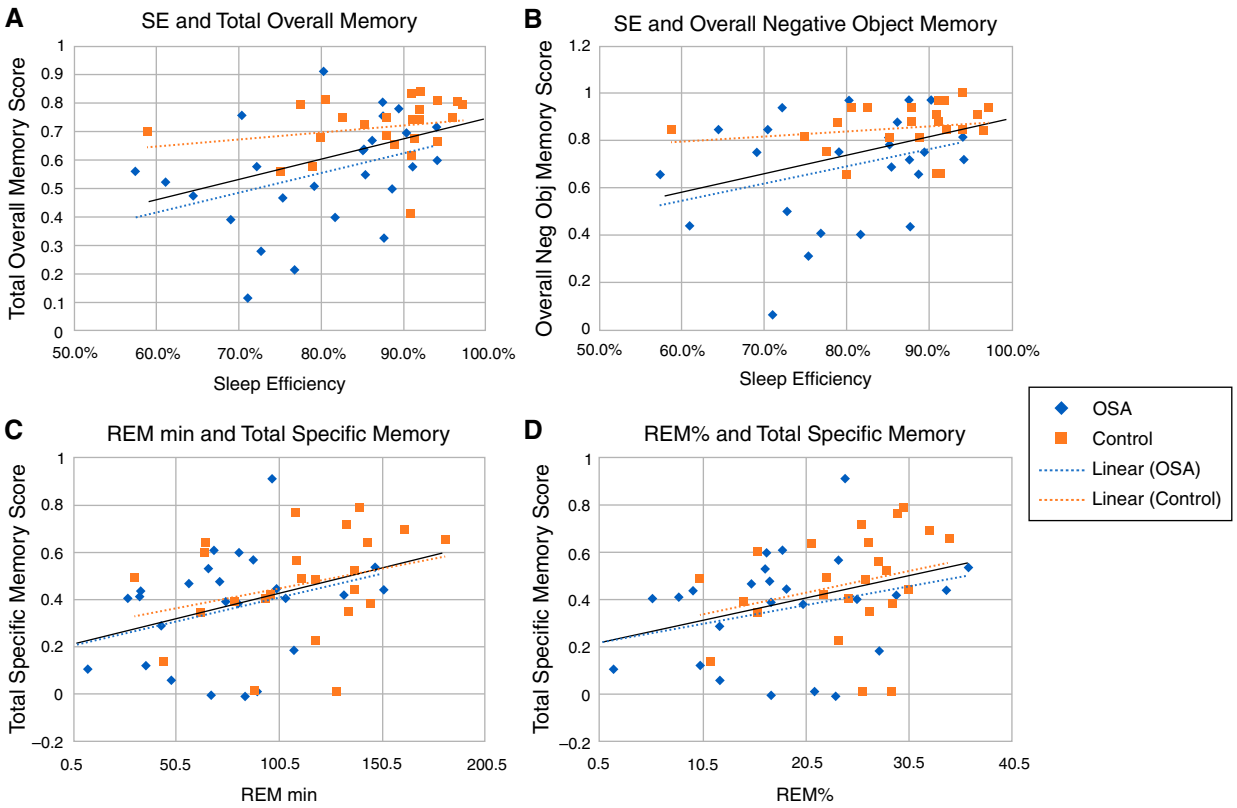

Figure 3. (*A*) The relationship between sleep efficiency and total overall memory scores. (*B*) The relationship between sleep efficiency and overall memory for negative objects. (*C*) The relationship between time of sleep spent in rapid eye movement (REM) and total specific memory. (*D*) The relationship between the percentage of sleep spent in REM and total specific memory. OSA = obstructive sleep apnea; REM% = percent of sleep spent in REM; REM min = number of minutes of REM sleep; SE = sleep efficiency.

Table 7. Sleep measure and memory correlations

		Overall Memory		Specific Memory	
		Negative Object Memory	**Total Overall Memory**	**Negative Object Memory**	**Total Specific Memory**
Sleep efficiency					
SE	*r*	0.383	0.427	0.291	0.223
	P	0.006*	0.002*	0.04†	0.12
WASO	*r*	−0.374	−0.399	−0.266	−0.187
	P	0.007*	0.004*	0.06	0.19
OSA-related symptoms					
AHI	*r*	−0.285	−0.256	−0.209	−0.21
	P	0.045†	0.072	0.146	0.146
REM-AHI	*r*	−0.258	−0.235	−0.174	−0.145
	P	0.071	0.10	0.23	0.314
REM sleep					
REM%	*r*	0.226	0.318	0.286	0.360
	P	0.114	0.024†	0.044†	0.010*
REM min	*r*	0.259	0.350	0.329	0.385
	P	0.069	0.013*	0.02†	0.006*

Definition of abbreviations: AHI = apnea–hypopnea index; OSA = obstructive sleep apnea; REM = rapid eye movement; REM% = percent of sleep spent in REM sleep; REM-AHI = apnea–hypopnea index during REM sleep; REM min = number of minutes of REM sleep; SE = sleep efficiency; WASO = wake after sleep onset.
Correlations between *a priori* selected measures of sleep (SE, OSA-related symptoms, and REM sleep metrics) and total memory and negative object memory were calculated both as overall and specific memory scores. *See* Table E1 for exploratory associations between all measures of sleep and emotional memory tradeoff memory performance.
*$P < 0.05$.
†$P < 0.017$ for Bonferroni correction.

moderate OSA symptoms. As such, further research should investigate the impact of OSA and REM-predominant OSA on emotional memory and emotion processing in groups with more severe OSA symptoms and more severe depression and how differences in degrees of stress may affect the encoding, retention, and recall of memories between patients with OSA and healthy control participants. Similarly, whereas the makeup of race and ethnicity were similar between groups, the sample was predominantly White and non-Hispanic, and as such, it will be important to replicate this study in more diverse populations (including different age groups) to determine the generalizability of these findings.

Conclusions

We found that OSA has a substantial negative impact on the processing and consolidation of emotional memory during sleep. Although overall memory showed impairments across all aspects of memory, regardless of valence or scene component, specific memory calculations showed a discrete impairment in the emotional elements of memory. Although our findings here are the first to demonstrate this effect in emotional memory processing during sleep, it adds to an extensive body of work on cognitive impairments in patients with OSA. These findings should be clearly articulated to patients with OSA as a means of promoting adherence to treatment. In addition, further investigation should determine the role that this deterioration in the specificity of negative memories may play in the onset and maintenance of negative mood symptoms frequently associated with OSA. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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