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Journal

Journal of Clinical Sleep Medicine, 16(3)

ISSN

1550-9389

Authors

Djonlagic, Ina
Guo, Meng
Igue, Moroke
et al.

Publication Date

2020-03-15

DOI

10.5664/jcsm.8210

Peer reviewed

https://doi.org/10.5664/jcsm.8210

JCSM | Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

REM-related obstructive sleep apnea: when does it matter? Effect on motor memory consolidation versus emotional health

Ina Djonlagic, MD[1,2]; Meng Guo, MD[1,3]; Moroke Igue, BS[1]; Atul Malhotra, MD[4]; Robert Stickgold, PhD[2]

[1]Department of Neurology, Beth Israel Hospital and Harvard Medical School, Boston, Massachusetts; [2]Center for Sleep and Cognition, Department of Psychiatry, Beth Israel Hospital and Harvard Medical School, Boston, Massachusetts; [3]Department of Plastic Surgery, Medical College of Wisconsin, Milwaukee, Wisconsin; [4]Division of Pulmonary, Critical Care and Sleep Medicine, University of California San Diego, La Jolla, California

Study Objectives: The clinical importance of obstructive sleep apnea, which can be prevalent during rapid eye movement (REM) sleep, is unclear. The current study examines the effect of REM-related obstructive sleep apnea on motor memory consolidation as well as on mood states.

Methods: We compared performance on the motor sequence task (MST), psychomotor vigilance test (PVT), Functional Outcomes of Sleep Questionnaire, and the Profile of Mood State (POMS) survey between 3 groups: healthy controls (n = 18), REM-exclusive OSA (n = 17), and patients with OSA with respiratory events throughout REM and non-rapid eye movement (NREM) sleep (n = 18).

Results: As expected, performance on the MST improved overnight in the healthy control group. An improvement which was similar in magnitude was also observed in the REM-exclusive OSA group whereas patients with similar OSA during REM and NREM sleep showed reduced overnight memory consolidation. Consistent with these results, we found a correlation between overnight MST improvement and the apnea hypopnea index during NREM sleep (P = .041), but not during REM sleep (P = .424). However, patients with REM-exclusive apnea demonstrated the most negative emotions based on scoring highest on the POMS survey (P = .019).

Conclusions: Our results provide evidence that although apneas occurring only during REM sleep do not have an effect on the encoding and stabilization of motor sequence memories, they are deleterious for emotional health.

Keywords: emotional help, lung, OSA, REM sleep, sleep-dependent memory consolidation

Citation: Djonlagic I, Guo M, Igue M, Malhotra A, Stickgold R. REM-related obstructive sleep apnea: when does it matter? Effect on motor memory consolidation versus emotional health. *J Clin Sleep Med*. 2020;16(3):377–384.

BRIEF SUMMARY

Current Knowledge/Study Rationale: The clinical significance of obstructive sleep apnea, which can occur exclusively or predominantly during REM sleep remains unclear and due to lack of consensus, patients with this condition remain largely untreated. This study was designed to demonstrate the distinctive effect of REM-related OSA on mood states compared to motor memory consolidation.

Study Impact: Although consolidation of motor memories remains unaffected, our results demonstrate a link between REM-related OSA and emotional health. This effect on outcome measures of emotional regulation provides support for approaching REM-related OSA as a distinct clinical entity and serves as an incentive to develop better diagnostic criteria and consider separate treatment guidelines.

INTRODUCTION

Although sleep apnea is often more pronounced during rapid eye movement (REM) sleep, the term "REM-related" sleep apnea has been used to label sleep-disordered breathing, which is either significantly worse or exclusively present during REM sleep. The prevalence of REM-related sleep apnea is thought to range from 14% to 37% among patients referred for sleep evaluation and was found to have an estimated prevalence of 40% in a middle- to older-age population sample.[1,2] Fluctuations of physiologic variables are a characteristic of REM sleep; however, REM sleep is also a period of vulnerability for an increased tendency of upper airway collapse due to diminished genioglossus activity secondary to the cholinergic mediated inhibition of hypoglossal motor output.[3,4]

This notion has raised the questions (1) to what extent fluctuations in tidal volume area physiologic feature of REM sleep and when do they transition into a respiratory disease requiring therapy and (2) whether we are dealing with a REM-state specific disorder or just a segment of the spectrum of sleep-disordered breathing, as REM-related apnea has been associated with milder disease and female sex.[5,6]

Outcome studies focusing on daytime sleepiness and quality of life in patients with REM-related obstructive sleep apnea (OSA) have not found a consistent association, whereas studies focusing on cardiometabolic outcomes have found links with incident hypertension, impaired glucose metabolism, and worsening of pre-existing cardiovascular disease.[7–14] Currently, the specific clinical importance of REM-related OSA continues to be unclear and thus treatment recommendations in the absence of non-rapid eye movement (NREM) OSA remain to be determined.

REM sleep has been known to be altered in depression and although several studies have pointed to OSA modulating mood symptoms, particularly major depressive disorders and increasing psychological distress, it remains unknown whether REM-related OSA would also result in mood alterations.[15,16]

Experimental manipulations of REM sleep in healthy humans by means of REM sleep deprivation or pharmacologic manipulation have demonstrated no decreases in procedural or declarative memory performances.[17,18] Specifically overnight improvement on motor tasks, such as a sequential finger-tapping task, has been shown to be predicted by the amount of N2-NREM sleep during the latter portion of the night.[19,20]

To support further the state-specific nature of NREM sleep to the consolidation of motor skill learning, we sought to test the hypothesis that OSA confined mainly to REM sleep does not impair motor memory consolidation and that observed deficits would be a function of disrupted NREM sleep. Based on the lack of studies investigating the effect of REM-related apnea on mood states we also tested the hypothesis that REM-related OSA will alter self-reported mood states as measured by the Profile of Mood State (POMS) questionnaire.

METHODS

Participants

We recruited 53 right-handed men and women, ages 25 to 70 years, from a local sleep clinic. All participants had been referred for overnight polysomnography (PSG). After PSG, participants were subdivided into three groups: healthy controls (HC, n = 18), REM-exclusive OSA (REM-OSA, n = 17), and those with respiratory events throughout REM and NREM sleep (REM/NREM OSA, n = 18). In order to qualify for the REM-exclusive group, based on previous literature the following a priori criteria were required to estimate precisely the severity of disordered breathing during REM sleep by using a combination of REM/NREM-apnea-hypopnea index (AHI) ratio, time spent in REM sleep, and OSA severity: AHI-REM/AHI-NREM ratio ≥ 2, AHI-NREM < 5 events/h, AHI-REM > 5 events/h with a minimum amount of 30 minutes REM sleep per recording.[9] Those participants in the REM/NREM-OSA group were required to have an AHI-REM/AHI-NREM ratio ≤ 2 and an AHI > 15 events/h based on larger outcome studies and to focus on clinically significant OSA.[21] Patients, who had been referred for a sleep study, but were found to have no significant sleep-disordered breathing, were assigned to the control group.

Exclusion criteria

Subjects were excluded if they (1) were found to have a periodic limb movement index > 15 events/h based on PSG, (2) had a central sleep apnea index > 5 events/h, (3) had another diagnosed sleep or circadian disorder, (4) had a history of alcohol, narcotic, or other drug abuse, (5) had a history of a medical, neurologic, or psychiatric disorder (other than OSA and treated hypertension) that could influence excessive daytime sleepiness, (6) used medications known to have an effect on sleep and daytime vigilance (eg, psychoactive drugs or medications, sedatives or hypnotics, including selective serotonin reuptake inhibitors), or (7) were left-handed.

Study design

In the evening, participants first performed a 5-minute version of the psychomotor vigilance task (PVT). The PVT objectively measures sustained attention and reaction time and has been shown to be sensitive to sleep deprivation, partial sleep loss, and circadian variation in performance, allowing us to control for differences in attention between groups.[22,23] During the task, participants are asked to push a button as fast as they can whenever they see a small (3 mm high, 4 digits wide) LED millisecond clock begin counting up from 0000. Pressing the button stops the digital clock, allowing the person 1.5 seconds to read the reaction time (RT). The interstimulus interval on the task varies randomly from 2 to 10 seconds and complete task duration can be either 5 minutes, as in our case, or 10 minutes.[24]

Following the PVT, participants were randomized to one of two sequences of the motor sequence task (MST).[19,25] During the MST, people are asked to type repeatedly a five-digit sequence on a standard computer keyboard with their nondominant (left) hand. The specific sequence to be typed is displayed on the computer screen at all times. Typing is performed in 30-second trials separated by 30-second rest periods. Training and retest each include 12 trials. Despite MST randomization prior to group assignment, MST sequences A and B were equally balanced across all three groups (sequence A, healthy control patients: 54%, REM-exclusive OSA: 46%, REM/NREM-OSA: 59%). Participants then filled out several questionnaires including the POMS questionnaire (score range: 0 to 260, higher scores indicate less stable mood profiles), Functional Outcomes of Sleep Questionnaire (FOSQ; score range: 2–120, higher scores indicate better functional status), Beck Depression Inventory (range: 0 to 63, higher scores indicate greater symptom severity), Epworth Sleepiness Scale (score range 0–24, higher scores indicate higher sleep propensity) and Stanford Sleepiness scale (score range 1–7, higher scores indicate more self-reported sleepiness) and subsequently spent the night in the laboratory where they underwent standard sleep recording.[26–29] The following morning, they repeated the PVT and were tested on the MST sequence from the evening before. As learning the motor sequence task is sequence specific with no transfer of learning to new sequences, participants then trained on a new MST sequence after a 10-minute break, allowing us to control for time-of-day effects on motor sequence learning and performance.[20]

Polysomnography

Standard overnight PSG recording and data interpretation were performed in accordance with the American Academy of Sleep Medicine scoring manual.[30,31] Recordings included standard electroencephalogram leads (F1, F2, C3, C4, O1, and O2), as well as bilateral electrooculogram, submental electromyogram, bilateral anterior tibialis electromyogram, and standard electrocardiogram electrodes. We also recorded nasal/oral airflow (thermistor), nasal pressure (Validyne transducer), chest plus abdominal wall motion (piezo electrodes), and oxygen saturation. All studies were scored by a registered PSG technologist blind to participant identification. For calculating the AHI,

Table 1—Demographic and polysomnographic characteristics of the three groups.

	Control Patients (n = 18)	NREM/REM-OSA (n = 18)	REM-OSA (n = 17)	*P*
Age (years)	36.2 ± 2.8	37.5 ± 3.0	37.2 ± 3.6	.957
Sex, female, n (%)	8 (44.4)	7 (39.0)	7 (41.2)	.693
BMI (kg/m^2)	26.4 ± 1.5	33.8 ± 1.3	31.8 ± 2.7	.148
TST (minutes)	344.3 ± 18.1	320.3 ± 9.6	365.4 ± 14.6	.074
Sleep efficiency (%)	83.9 ± 4.2	82.2 ± 2.7	79.1 ± 4.1	.663
Stage N1 sleep (%TST)	7.81 ± 1.8	9.6 ± 1.3	6.0 ± 1.8	.189
Stage N2 sleep (%TST)	62.0 ± 3.3	60.0 ± 1.4	64.4 ± 2.4	.415
Stage N3 sleep (%TST)	9.3 ± 2.5	12.2 ± 1.8	9.8 ± 1.4	.285
Stage R sleep (%TST)	20.9 ± 2.2	18.1 ± 1.3	20.2 ± 2.1	.256
AHI total (events/h)	3.0 ± 0.7	17.8 ± 2.0	6.0 ± 1.2	< .001* ‡
AHI NREM (events/h)	3.4 ± 0.7	17.4 ± 1.9	3.3 ± 0.3	< .001* ‡
AHI REM (events/h)	3.7 ± 0.6	18.7 ± 3.6	19.1 ± 3.6	< .001* †
Oxygen nadir (%)	91.6 ± 0.6	87.8 ± 0.9	86.8 ± 2.1	.041†
Arousal index (events/h)	16.2 ± 1.7	24.5 ± 1.7	18.8 ± 2.0	< .001*
PLMS index (events/h)	1.0 ± 0.6	2.9 ± 0.9	1.7 ± 0.9	.263

Values are presented as mean ± standard error of the mean. *P* represents results of analysis of variance across the three groups for each measure. Symbols indicate significant pairwise comparisons: *control patients versus NREM/REM-OSA; †control patients versus REM-OSA; ‡NREM/REM-OSA versus REM-OSA. AHI = apnea-hypopnea index, BMI = body mass index, NREM = non-rapid eye movement, OSA = obstructive sleep apnea, PLMS = periodic limb movements of sleep, REM = rapid eye movement, TST = total sleep time.

hypopneas were defined as abnormal respiratory events lasting at least 10 seconds and associated with at least a 30% reduction in respiratory effort or airflow along with either an oxygen desaturation > 3% or an arousal lasting ≥ 10 seconds.

Statistical analysis

One-way analysis of variance (ANOVA) was performed to compare demographic, questionnaire, and PSG-derived sleep data. In case of significance this was followed post hoc by Tukey honestly significant difference (HSD) tests. Logistic regression analyses were performed to examine the correlation of sleep-related parameters with outcome measures. The main MST performance measure was the number of correctly typed sequences per 30-second trial, thus reflecting both speed and accuracy. Overnight MST improvement was calculated as percent change in performance speed (correct sequences per 30-second trial) for initial and plateau improvement taking into account the characteristic performance curves over the 12 training trials and 12 test trials [initial improvement = percent increase in performance from the last three training trials in the evening to the first three test trials in the morning, and plateau improvement = percent improvement from the last 6 training trials in the evening to the last 6 test trials in the morning].

Statistical analysis was performed using Stata (StataCorp 2013, Stata Statistical Software: Release 13, StataCorp LP, College Station, Texas). A value of $P < .05$ was considered significant. Variability is expressed as standard error of the mean.

Ethics statement

All participants provided written informed consent. The study was approved by the Partners' Institutional Review Board.

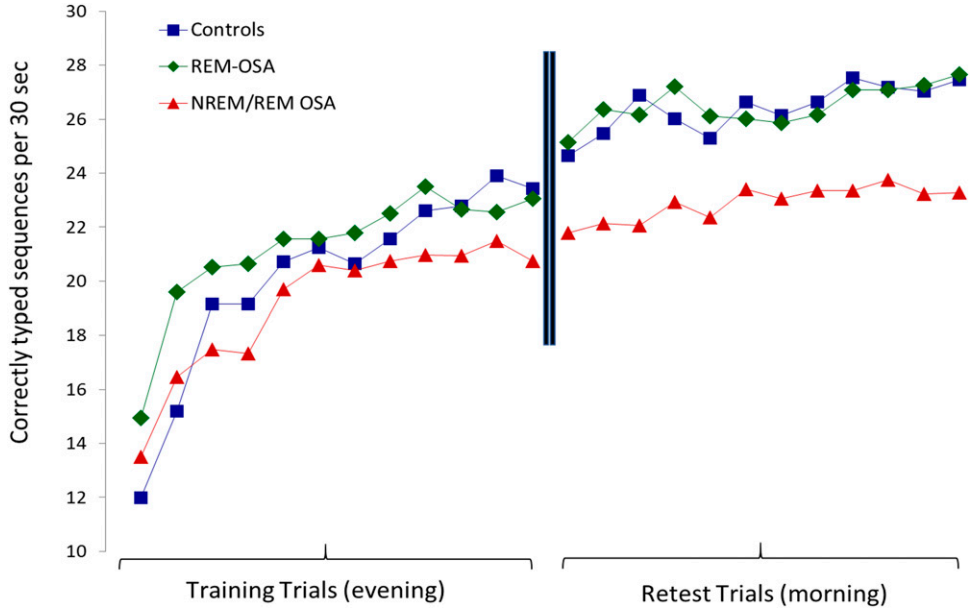
RESULTS

Demographic and polysomnographic data

Demographic and polysomnographic characteristics of the three groups are shown in **Table 1**. Among the three groups, there was no significant difference in age or body mass index. Measures of sleep architecture including total sleep time, sleep efficiency, and sleep stage distribution did not show significant differences. ANOVA among the three groups yielded significant differences for overall AHI ($P < .001$), NREM-AHI ($P < .001$) and REM-AHI ($P < .001$). Group differences were not determined by positional dependency of OSA. Post hoc Tukey HSD comparisons revealed significant differences for the REM-OSA and NREM/REM-OSA group comparisons of AHI ($P < .002$) and NREM-AHI ($P < .001$) as well as for the healthy control and NREM/REM-OSA group comparisons of AHI and NREM-AHI (both $P < .001$). For the REM-AHI, there were significant differences between the healthy control and NREM/REM-OSA groups ($P = .004$) and healthy control and REM-OSA groups ($P = .006$) comparisons but not for the comparison of the two OSA groups ($P = .996$). Significant group differences were also found for the arousal index ($P < .001$) with the post hoc Turkey HSD showing that only healthy control patients and patients with NREM/REM-OSA differed significantly ($P = .007$).

There was also a significant difference for the oxygen nadir among the three groups ($P = .041$) with Tukey HSD post hoc paired comparisons revealing a significant difference only between the healthy control and REM-OSA groups ($P = .043$) but not the comparison of healthy control and

Figure 1—Motor sequence test (MST) learning across 12 training trials in the evening and 12 test trials in the morning.



Healthy control participants (n = 18, blue squares), patients with rapid eye movement-exclusive obstructive sleep apnea (REM-OSA, n = 17, green diamonds) patients with obstructive sleep apnea during non-rapid eye movement and REM sleep (NREM/REM OSA, n = 18, red triangles). Data points for each trial represent the group average. The y-axes represent the number of correct sequences typed in each 30-second epoch.

REM/NREM-OSA groups ($P = .131$) or the NREM/REM-OSA and REM-OSA group comparison ($P = .859$).

Motor sequence task

Practice-dependent improvement during the initial evening training session is measured as the increase in correctly typed sequences from the first two trials to the average of the last three trials of the evening training session. All three groups demonstrated improvement across the 12 initial learning trials in the evening. Healthy control patients improved by 74% ± 9%, the NREM/REM-OSA group by 51% ± 8% and the REM-OSA group by 55% ± 18% (**Figure 1**).

As previously published, we calculated two measures of overnight improvement: (1) immediate improvement, which is the percent increase in performance from the last three training trials in the evening to the first three test trials in the morning, and (2) plateau improvement, which is the percentage of improvement from the last six training trials in the evening to the last six test trials the following morning.

The overall ANOVA showed significant differences in MST performance improvement for immediate ($P = .012$) and plateau improvement ($P = .009$). Healthy control patients showed a 10.9% ± 2.8% increase for immediate improvement and 21.8% ± 5.2% for plateau improvement. An improvement similar in magnitude was also observed in the REM-exclusive OSA group with 11.5% ± 4.7% and 22.0% ± 3.6% respectively (post hoc Tukey HSD, P [immediate improvement] = .25, P [plateau improvement] = .99). In contrast, patients with REM/NREM-OSA had only a 4.4% ± 2.9% overnight immediate improvement (post hoc Tukey HSD, P [versus healthy control patients] = .008), P [versus REM-OSA] = .34) and 8.9 ± 1.2 plateau improvement (post hoc Tukey HSD, P [versus healthy control patients] = .025), P [versus REM-OSA] = .023) (**Figure 2**).

Overnight MST improvement correlated with NREM-AHI ($P = .041$), but not REM-AHI ($P = .424$). Overnight learning improvement was not associated with arousal index ($P = .583$) or oxygen nadir ($P = .502$).

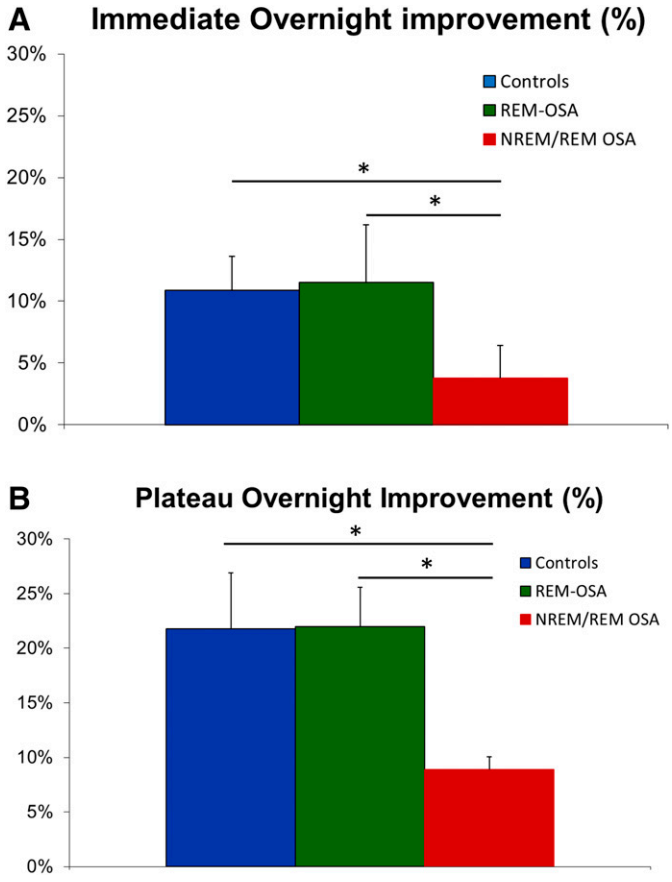
To assess if MST performance varied by time of the day, we asked all participants to train on a new MST sequence in the morning. All three groups showed very similar practice-dependent performance for the new MST sequence ($P = .94$) (**Figure S1** in the supplemental material).

Questionnaire data

There were significant group differences between the total score on the POMS questionnaire ($P = .019$; **Table 2**). Pairwise comparisons found that the scores of the REM-OSA group were significantly higher (more negative) than for healthy control patients ($P = .015$). Group comparisons between the REM-OSA and NREM/REM-OSA group did not reveal a significant difference ($P = .538$). Further subscale analysis revealed significant differences between the three groups in the areas of tension ($P = .052$), depression ($P = .034$), fatigue ($P = .005$) and total mood disturbance [total mood disturbance = tension + depression + anger + fatigue + confusion – vigor] ($P = .002$) and a trend difference for vigor ($P = .065$; **Figure 3** and **Table S1** in the supplemental material). There was a trend toward association between POMS scores and REM-AHI ($P = .061$) and a significant association between AHI-REM/AHI-NREM ratio and POMS scores ($P = .006$).

Post hoc Tukey HSD revealed a significant difference between healthy control patients and the REM-OSA group for

Figure 2—Initial and plateau improvements.



(A) Healthy control patients and those with rapid eye movement-obstructive sleep apnea (REM-OSA) show significantly more initial improvement (percent increase in performance from the last three training trials in the evening to the first three test trials in the morning) compared to patients with OSA during non-rapid eye movement and REM sleep (NREM/REM OSA), $P = .04$). *$P < .05$. **(B)** Healthy control patients and those with REM-OSA show significantly more plateau improvement (percent improvement from the last six training trials in the evening to the last six test trials in the morning) compared to patients with NREM/REM OSA ($P = .01$). *$P < .05$

tension ($P = .043$), depression ($P = .033$), fatigue ($P = .005$), and total mood disturbance (.002) but not vigor and confusion. Differences in subscales between the REM-OSA and NREM/REM-OSA group were present for fatigue ($P = .030$) and total mood disturbance ($P = .036$) only.

For the Beck Depression inventory, we found no significant differences between the three groups ($P = .606$). Furthermore, no significant differences were observed for self-reported sleepiness scales (Stanford Sleepiness Scale and Epworth Sleepiness Scales) or for the FOSQ.

PVT data

In the evening, mean PVT reaction time for healthy control patients was 383 ± 29 msec (lapses 5.8 ± 2.1), for NREM/REM-OSA 376 ± 28 msec (lapses 6.6 ± 2.5), and for REM-exclusive OSA 367 ± 28 msec (lapses 5.0 ± 2.6), and the three groups did not differ significantly (P [RT] = .475, P [lapses] = .892). All groups showed slower reaction times in the morning but again did not differ significantly (healthy controls = 436 ± 42 msec [lapses 7.9 ± 2.4)]; NREM/REM OSA = 442 ± 37 msec [lapses 10.7 ± 3.3]; REM-exclusive OSA = 425 ± 66 msec [lapses 8.0 ± 2.9] (P [RT] = .968, P [lapses] = .274).

DISCUSSION

Research has provided support for the role of specific sleep stages in facilitating an optimal consolidation of various memories.[32,33] Our study provides further proof that NREM sleep fragmentation is detrimental to overnight motor memory consolidation, but that REM sleep fragmentation (and related OSA) is less critical. All three groups showed practice-dependent improvement during the evening training trials and when learning a new sequence in the morning, suggesting that this finding is not due to a deficit in initial encoding, but a subsequent consolidation process.

As all three groups were similar in their rating of self-reported sleepiness as well as PVT-derived assessment of attention and vigilance in the evening and morning, there is supportive evidence for a link between sleep apnea and memory impairment, rather than poor MST performance being caused by general OSA-induced sleepiness or reduced attention.

Correlative studies have found an association between REM sleep and consolidation of procedural, spatial, and emotional memories.[34–38] However, pharmacologic suppression of REM sleep has not resulted in a decrease of declarative or procedural learning.[18,39] Selectively isolating the effect of pharmacological manipulation on REM sleep is challenging due to the state-independent alterations of neurotransmitters by certain antidepressants, some of which have been shown to have enhancing effects on memory functions, particularly those that have been shown to inhibit noradrenaline reuptake.[40]

Selective REM-deprivation studies have varied in results depending on memory tests applied but have been criticized due to the simultaneous induction of additional arousal, emotional irritation, and stress.[41,42]

Studying REM-related OSA offers an elegant noninvasive way of assessing the effect of REM-specific sleep fragmentation. In our participants, similar REM AHIs were present in the NREM/REM-OSA and REM-OSA group, ensuring that the difference between the two apnea groups was exclusively based only on the apnea-related sleep disruption ratio between NREM and REM sleep.

In agreement with earlier studies, patients with REM-OSA did not demonstrate increased scores for self-reported sleepiness or on the FOSQ.[43,44] Based on the difference in sleep quality, it was surprising that our three groups did not rate their self-reported sleepiness differently. This finding may in part be due to the referral bias inherent in a clinic-based sample. Thus, most participants will likely have complained of daytime fatigue or sleepiness which can be multifactorial and due to other unidentified, nonsleep-related processes.

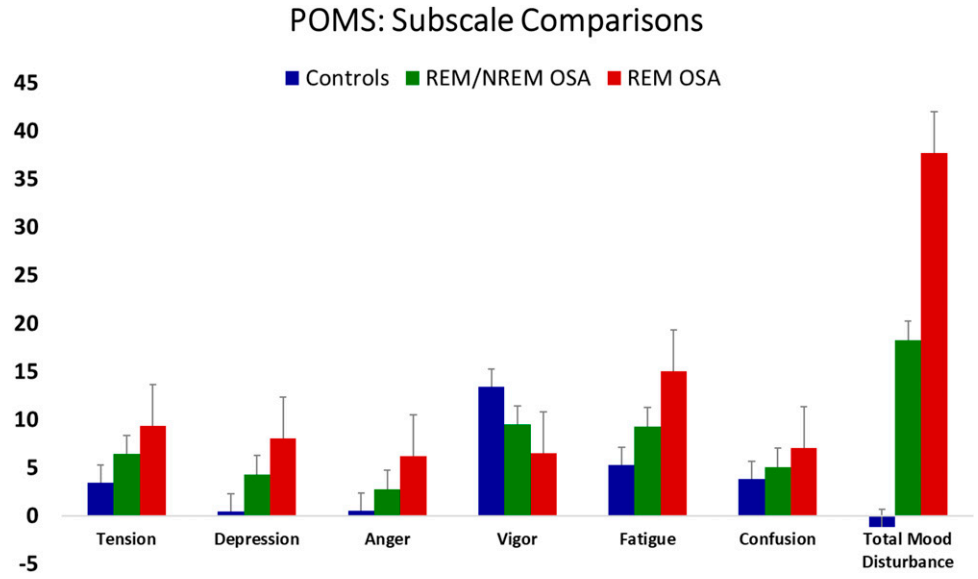
Insufficient sleep and sleep-disturbances resulting from sleep disorders have been tied to emotional dysregulation and psychiatric disorders.[45] Reported REM sleep abnormalities in depressed patient have mainly included a reduced REM sleep latency and REM-sleep density and, due to their persistence

Table 2—Questionnaire data from the three groups.

	Control Patients (n = 18)	NREM/REM-OSA (n = 18)	REM-OSA (n = 17)	*P*
ESS	7 ± 1.2	9.6 ± 1.4	8.6 ± 1.5	.438
Stanford Sleepiness Scale (PM)	2.7 ± 0.3	3.5 ± 0.3	3.3 ± 0.4	.135
Stanford Sleepiness Scale (AM)	2.8 ± 0.3	3.2 ± 0.3	3.4 ± 0.5	.498
FOSQ	96.2 ± 7.7	91.4 ± 4.1	91.8 ± 10.2	.878
BDI	3.1 ± 1.4	4.9 ± 1.8	6.9 ± 3.6	.606
POMS	43.8 ± 2.6	51 ± 4.0	65.6 ± 7.7	.019†

Values are presented as mean ± standard error of the mean. *P* represents results of analysis of variance across the three groups for each measure. Symbols indicate significant pairwise comparisons: *control patients versus NREM/REM-OSA; †control patients versus REM-OSA; ‡NREM/REM-OSA versus REM-OSA. BDI = Beck Depression Inventory, ESS = Epworth Sleepiness Scale, FOSQ = Functional Outcomes of Sleep Questionnaire = NREM = non-rapid eye movement, OSA = obstructive sleep apnea, POMS = Profile of Mood State questionnaire, REM = rapid eye movement.

Figure 3—Profile of Mood Scale subscales.



Among healthy control patients and patients with REM/NREM OSA and REM-OSA show significant differences in the areas of tension (*P* = .052), depression (*P* = .034), fatigue (*P* = .005), and total mood disturbance (*P* = .002) and a trend difference for vigor (*P* = .065).

even during disease remission, they have been considered to represent a marker for susceptibility to mood disorders.[46,47] Positron emission tomography imaging has shown increased regional blood flow in various areas during REM sleep, including pontine tegmentum, left thalamus, both amygdaloid complexes, anterior cingulate cortex, and right parietal operculum.[48,49] The activation pattern of the amygdala has been considered the neuroanatomic basis of the emotional memory processing during REM sleep.[50,51]

To our knowledge, our study is the first to examine the effect of REM-related OSA on emotional state. Our results are in line with a recent publication in adolescents, which found that increased REM fragmentation was independently associated with higher depression scores and a polygenic risk score for somatic complaints.[52] The specific processes underlying these associations remain unidentified, but previous models of REM sleep have proposed that REM sleep reduces the emotional tone originally associated with prior waking salient experiences, due to the reduction in adrenergic activity during REM sleep.[36] Although the NREM/REM-OSA group experienced similar REM sleep fragmentation, the significant association between AHI-REM/AHI-NREM ratio and POMS scores could potentially reflect a different proportion of downgrading in adrenergic activity from NREM to REM sleep, which in turn could affect the emotional regulatory processes during REM sleep.

Previous research has shown that specific sleep stages are critical for distinct processes in the consolidation of specific memory aspects. Given that consolidation of the MST has been connected to NREM sleep (mediated via sleep spindles), but not REM sleep, our results are consistent with our initial hypothesis that NREM sleep fragmentation as seen in the NREM/REM group would result in reduced overnight MST improvement while remaining unaffected by the isolated REM sleep fragmentation as seen in the REM-OSA group.

Based on the clear association of REM sleep fragmentation and REM-NREM ratio of fragmentation with POMS scores

in our analyses, we propose that OSA-related REM sleep fragmentation reflects a distinct clinical phenomenon within the larger spectrum of sleep-disordered breathing.

The difference in clinical outcomes between NREM and REM sleep fragmentation argues for reconsidering traditional sleep apnea definitions and clinical treatment thresholds, as patients may be better served by separating their apnea hypopnea index into NREM- and REM-specific indices. Moreover, the recent move toward home sleep testing, which has been driven by financial considerations, may well obscure these important considerations. By applying the overall AHI only, we may be missing out on patients who have important REM OSA and who do not meet the AHI insurance criteria for CPAP but based on our findings might still benefit from treatment.

Despite the strength of our study, we acknowledge a number of limitations. First, our sample size was relatively modest due to the labor-intensive nature of our measurements. However, our study was adequately powered for our primary outcome measurements based on values from our previous studies and can use current data to design subsequent studies. Second, we studied a referral sample sent to our sleep laboratory and therefore our findings may not generalize to other populations, for example, community-based samples. In theory, patients who come to the clinic with REM-related apnea may be the subset of individuals who are susceptible to these events. However, other asymptomatic patients may never come to the clinic. Thus, further work would be required to assess the full spectrum of patients with REM-related respiratory abnormalities.

Third, our participants had a broad range in age, and included both men and women without further characterization. Our results may therefore have been affected by hormonal changes in women and other unknown physiological features, though both groups included a similar ratio of men and women.[53]

Given that the NREM/REM-OSA group had overall more respiratory events across the night compared to the REM-OSA group, we can therefore not rule out with absolute certainty that the reduced overnight improvement on the MST is solely based on fragmented NREM sleep, although previous research has indicated the importance of N2 sleep in consolidating this type of procedural motor memory.[19,20]

Finally, we have focused on the motor sequence task because we have considerable experience with this test and it showed excellent discriminative function in prior OSA studies.

Because a variety of memory tests involve different brain centers (eg, motor or visual cortex, medial temporal lobe or hippocampus), we advocate for further research into memory tasks dependent on these brain centers and how they may be affected by REM-related apnea.

CONCLUSIONS

Different aspects of sleep are important to a number of brain functions. Our study provides support for the connection between REM sleep and emotional health as well as the inherent differences of NREM versus REM sleep and their association with the stabilization and enhancement of motor memories.

ABBREVIATIONS

AHI, apnea-hypopnea index
ANOVA, analysis of variance
FOSQ, Functional Outcomes of Sleep Questionnaire
MST, motor sequence task
NREM, non-rapid eye movement
OSA, obstructive sleep apnea
POMS, Profile of Mood State
PSG, polysomnography
PVT, psychomotor vigilance test
REM, rapid eye movement

REFERENCES

1. Conwell W, Patel B, Doeing D, et al. Prevalence, clinical features, and CPAP adherence in REM-related sleep-disordered breathing: a cross-sectional analysis of a large clinical population. *Sleep Breath*. 2012;16(2):519–526.
2. Acosta-Castro P, Hirotsu C, Marti-Soler H, et al. REM-associated sleep apnoea: prevalence and clinical significance in the HypnoLaus cohort. *Eur Respir J*. 2018;52(2):1702484.
3. Grace KP, Hughes SW, Horner RL. Identification of the mechanism mediating genioglossus muscle suppression in REM sleep. *Am J Respir Crit Care Med*. 2013;187(3):311–319.
4. McSharry DG, Saboisky JP, Deyoung P, et al. Physiological mechanisms of upper airway hypotonia during REM sleep. *Sleep*. 2014;37(3):561–569.
5. Koo BB, Patel SR, Strohl K, Hoffstein V. Rapid eye movement-related sleep-disordered breathing: influence of age and gender. *Chest*. 2008;134(6):1156–1161.
6. O'Connor C, Thornley KS, Hanly PJ. Gender differences in the polysomnographic features of obstructive sleep apnea. *Am J Respir Crit Care Med*. 2000;161(5):1465–1472.
7. Kass JE, Akers SM, Bartter TC, Pratter MR. Rapid-eye-movement-specific sleep-disordered breathing: a possible cause of excessive daytime sleepiness. *Am J Respir Crit Care Med*. 1996;154(1):167–169.
8. Punjabi NM, Bandeen-Roche K, Marx JJ, Neubauer DN, Smith PL, Schwartz AR. The association between daytime sleepiness and sleep-disordered breathing in NREM and REM sleep. *Sleep*. 2002;25(3):307–314.
9. Mokhlesi B, Punjabi NM. "REM-related" obstructive sleep apnea: an epiphenomenon or a clinically important entity? *Sleep*. 2012;35(1):5–7.
10. Chervin RD, Aldrich MS. The relation between multiple sleep latency test findings and the frequency of apneic events in REM and non-REM sleep. *Chest*. 1998;113(4):980–984.
11. Chami HA, Baldwin CM, Silverman A, et al. Sleepiness, quality of life, and sleep maintenance in REM versus non-REM sleep-disordered breathing. *Am J Respir Crit Care Med*. 2010;181(9):997–1002.
12. Aurora RN, Crainiceanu C, Gottlieb DJ, Kim JS, Punjabi NM. Obstructive sleep apnea during REM sleep and cardiovascular disease. *Am J Respir Crit Care Med*. 2018;197(5):653–660.
13. Mokhlesi B, Finn LA, Hagen EW, et al. Obstructive sleep apnea during REM sleep and hypertension. results of the Wisconsin Sleep Cohort. *Am J Respir Crit Care Med*. 2014;190(10):1158–1167.
14. Chami HA, Gottlieb DJ, Redline S, Punjabi NM. Association between glucose metabolism and sleep-disordered breathing during REM sleep. *Am J Respir Crit Care Med*. 2015;192(9):1118–1126.
15. Peppard PE, Szklo-Coxe M, Hla KM, Young T. Longitudinal association of sleep-related breathing disorder and depression. *Arch Intern Med*. 2006;166(16):1709–1715.
16. Aloia MS, Arnedt JT, Smith L, Skrekas J, Stanchina M, Millman RP. Examining the construct of depression in obstructive sleep apnea syndrome. *Sleep Med*. 2005;6(2):115–121.

17. Hornung OP, Regen F, Danker-Hopfe H, Schredl M, Heuser I. The relationship between REM sleep and memory consolidation in old age and effects of cholinergic medication. *Biol Psychiatry*. 2007;61(6):750–757.
18. Rasch B, Pommer J, Diekelmann S, Born J. Pharmacological REM sleep suppression paradoxically improves rather than impairs skill memory. *Nat Neurosci*. 2009;12(4):396–397.
19. Walker MP, Brakefield T, Morgan A, Hobson JA, Stickgold R. Practice with sleep makes perfect: sleep-dependent motor skill learning. *Neuron*. 2002;35(1):205–211.
20. Fischer S, Hallschmid M, Elsner AL, Born J. Sleep forms memory for finger skills. *Proc Natl Acad Sci USA*. 2002;99(18):11987–11991.
21. Young T, Palta M, Dempsey J, Peppard PE, Nieto FJ, Hla KM. Burden of sleep apnea: rationale, design, and major findings of the Wisconsin Sleep Cohort study. *WMJ*. 2009;108(5):246–249.
22. Van Dongen HP, Maislin G, Mullington JM, Dinges DF. The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep*. 2003;26(2):117–126.
23. Dinges DF, Powell JW. Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. *Behav Res Methods Instrum Comput*. 1985;17(6):652–655.
24. Roach GD, Dawson D, Lamond N. Can a shorter psychomotor vigilance task be used as a reasonable substitute for the ten-minute psychomotor vigilance task? *Chronobiol Int*. 2006;23(6):1379–1387.
25. Karni A, Meyer G, Rey-Hipolito C, et al. The acquisition of skilled motor performance: fast and slow experience-driven changes in primary motor cortex. *Proc Natl Acad Sci U S A*. 1998;95(3):861–868.
26. McNair DMLM, Droppleman LF. *Revised manual for the Profile of Mood States*. San Diego, CA: Educational and Industrial Testing Service; 1992.
27. Weaver TE, Laizner AM, Evans LK, et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. *Sleep*. 1997;20(10):835–843.
28. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991;14(6):540–545.
29. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961;4(6):561–571.
30. 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.
31. Anbar RD, Hehir DA. Hypnosis as a diagnostic modality for vocal cord dysfunction. *Pediatrics*. 2000;106(6):E81.
32. Stickgold R. Sleep-dependent memory consolidation. *Nature*. 2005;437(7063):1272–1278.
33. Diekelmann S, Born J. The memory function of sleep. *Nat Rev Neurosci*. 2010;11(2):114–126.
34. Groch S, Wilhelm I, Diekelmann S, Born J. The role of REM sleep in the processing of emotional memories: evidence from behavior and event-related potentials. *Neurobiol Learn Mem*. 2013;99:1–9.
35. Payne JD, Stickgold R, Swanberg K, Kensinger EA. Sleep preferentially enhances memory for emotional components of scenes. *Psychol Sci*. 2008;19(8):781–788.
36. van der Helm E, Yao J, Dutt S, Rao V, Saletin JM, Walker MP. REM sleep depotentiates amygdala activity to previous emotional experiences. *Curr Biol*. 2011;21(23):2029–2032.
37. Plihal W, Born J. Effects of early and late nocturnal sleep on declarative and procedural memory. *J Cogn Neurosci*. 1997;9(4):534–547.
38. Plihal W, Born J. Effects of early and late nocturnal sleep on priming and spatial memory. *Psychophysiology*. 1999;36(5):571–582.
39. Göder R, Seeck-Hirschner M, Stingele K, et al. Sleep and cognition at baseline and the effects of REM sleep diminution after 1 week of antidepressive treatment in patients with depression. *J Sleep Res*. 2011;20(4):544–551.
40. Feltmann K, Konradsson-Geuken A, De Bundel D, Lindskog M, Schilstrom B. Antidepressant drugs specifically inhibiting noradrenaline reuptake enhance recognition memory in rats. *Behav Neurosci*. 2015;129(6):701–708.
41. Genzel L, Dresler M, Wehrle R, Grozinger M, Steiger A. Slow wave sleep and REM sleep awakenings do not affect sleep dependent memory consolidation. *Sleep*. 2009;32(3):302–310.
42. Karni A, Tanne D, Rubenstein BS, Askenasy JJ, Sagi D. Dependence on REM sleep of overnight improvement of a perceptual skill. *Science*. 1994;265(5172):679–682.
43. Khan A, Harrison SL, Kezirian EJ, et al. Obstructive sleep apnea during rapid eye movement sleep, daytime sleepiness, and quality of life in older men in Osteoporotic Fractures in Men (MrOS) Sleep Study. *J Clin Sleep Med*. 2013;9(3):191–198.
44. Su CS, Liu KT, Panjapornpon K, Andrews N, Foldvary-Schaefer N. Functional outcomes in patients with REM-related obstructive sleep apnea treated with positive airway pressure therapy. *J Clin Sleep Med*. 2012;8(3):243–247.
45. Benca RM, Obermeyer WH, Thisted RA, Gillin JC. Sleep and psychiatric disorders. A meta-analysis. *Arch Gen Psychiatry*. 1992;49(8):651–668, discussion 669-670.
46. Benca RM, Peterson MJ. Insomnia and depression. *Sleep Med*. 2008;9(Suppl 1):S3–S9.
47. Giles DE, Roffwarg HP, Rush AJ. A cross-sectional study of the effects of depression on REM latency. *Biol Psychiatry*. 1990;28(8):697–704.
48. Maquet P, Peters J, Aerts J, et al. Functional neuroanatomy of human rapid-eye-movement sleep and dreaming. *Nature*. 1996;383(6596):163–166.
49. Nofzinger EA, Mintun MA, Wiseman M, Kupfer DJ, Moore RY. Forebrain activation in REM sleep: an FDG PET study. *Brain Res*. 1997;770(1-2):192–201.
50. McGaugh JL. The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annu Rev Neurosci*. 2004;27(1):1–28.
51. Corsi-Cabrera M, Velasco F, Del Rio-Portilla Y, et al. Human amygdala activation during rapid eye movements of rapid eye movement sleep: an intracranial study. *J Sleep Res*. 2016;25(5):576–582.
52. Pesonen AK, Gradisar M, Kuula L, et al. REM sleep fragmentation associated with depressive symptoms and genetic risk for depression in a community-based sample of adolescents. *J Affect Disord*. 2019;245:757–763.
53. Mano M, Hoshino T, Sasanabe R, et al. Impact of gender and age on rapid eye movement-related obstructive sleep apnea: a clinical study of 3234 Japanese OSA patients. *Int J Environ Res Public Health*. 2019;16(6):1068.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication May 3, 2019
Submitted in final revised form October 29, 2019
Accepted for publication October 29, 2019
Address correspondence to: Ina Djonlagic, MD, Department of Neurology, Beth Israel Deaconess Medical Center, 330 Brookline Avenue/KS 434, Boston MA 02115; Tel: (617) 667-5129; Fax: (617) 667-5216; Email: idjonlag@bidmc.harvard.edu

DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. Work for this study was performed at Brigham and Women's Hospital and Beth Israel Deaconess Medical center in Boston, MA. This study was funded by NIH grant # K23HL103850 and American Sleep Medicine Foundation grant #54-JF-10 (PI both, Ina Djonlagic). Dr. Malhotra is PI on NIH R01 HL085188, K24 HL132105, T32HL134632 and co-investigator on R21 HL121794, R01 HL119201, R01 HL081823. As an Officer of the American Thoracic Society, Dr. Malhotra has relinquished all outside personal income since 2012. ResMed, Inc. provided a philanthropic donation to the UC San Diego. The authors report no conflicts of interest.