2017-11

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Sleep Medicine 43 (2018) 71–76

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Elevated tau and interleukin-6 concentrations in adults with obstructive sleep apnea

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ARTICLE INFO

Article history:
Received 31 July 2017
Received in revised form
4 November 2017
Accepted 10 November 2017
Available online 24 November 2017

Keywords:
Tau
Interleukin-6 (IL-6)
Obstructive sleep apnea (OSA)
Biomarkers
Neurodegeneration
Inflammation

ABSTRACT

Obstructive sleep apnea (OSA) is characterized by apneas and hypopneas that result in hypoxia, cerebral hypoperfusion, endothelial dysfunction, inflammation, and oxidative stress. These pathophysiologic processes likely contribute to neuronal damage. Tau is a protein that stabilizes microtubules and, along with amyloid beta (Aβ), is associated with neurodegenerative processes. We sought to determine if tau and other biomarkers of inflammation were related to OSA severity.

Concentrations of tau, Aβ40, Aβ42, c-reactive protein (CRP), TNF-α, interleukin (IL)-6, and IL-10 were measured in blood and compared between participants with moderate-severe OSA (n = 28), those with mild OSA (n = 22), and healthy controls (n = 24). The cohort included relatively young, primarily male active duty military personnel without a history of traumatic brain injury or neurodegenerative disease. Total biomarker concentrations were determined from plasma samples using an ultra-sensitive detection method, Simoa™, and CRP was assayed by ELISA. Total tau and IL-6 concentrations were elevated in participants with moderate-severe OSA, with a mean apnea-hypopnea index (AHI) of 26.1/h, compared to those with mild OSA (mean AHI 8.6/h) and healthy controls (mean AHI 2.1/h). Tau concentrations were also significantly correlated with the AHI ($r = 0.342$, $p = 0.004$). Our findings show that tau is elevated in the blood of young patients with moderate-severe OSA, suggesting that this degree of sleep-disordered breathing is a contributing factor in the development of neurodegenerative disorders. The finding of increased IL-6 further suggests that inflammatory biomarkers are present early in the course of this chronic disease.

1. Introduction

Obstructive sleep apnea (OSA) is a highly prevalent disorder, found in up to 30% of males between the ages of 30 and 70 [1]. OSA is characterized by repetitive episodes of partial or complete upper airway obstruction during sleep [2] and can result in intermittent hypoxia and fragmented sleep [3]. These processes can cause microstructural vascular injuries and oxidative stress [4] that may increase the risk for cognitive deficits, even in young patients [5,6]. Supporting this, evidence of white matter changes are observed in patients with OSA [7], suggesting that OSA may cause neuronal damage.

Tau is a microtubule-associated protein that functions as a structural element in the axonal cytoskeleton and is necessary for normal neuronal activity [8,9]. At low levels, amyloid-beta (Aβ) functions to maintain neuronal growth, synaptic activity, and survival [10]; however, at high enough levels, Aβ forms aggregates and eventually neurofibrillary plaques that have significant implications for cognitive deficits [11,12]. A recent study reported elevated concentrations of phosphorylated-tau (p-tau) and Aβ40, Aβ42, and total Aβ levels in middle-aged cognitively normal OSA patients (mean age = 44.31) compared to healthy controls [13]. Additionally,

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https://doi.org/10.1016/j.sleep.2017.11.1121

in the cerebrospinal fluid (CSF), higher total tau/Aβ42 levels were associated with OSA and cognitive impairments in elderly patients (mean age = 67.96) [14]. In a study assessing healthy children and children with a diagnosis of obesity, OSA, and obesity + OSA, children with a diagnosis of OSA and obesity + OSA had significantly elevated blood levels of Alzheimer's disease (AD)-related proteins, Aβ42, and presenilin-1 (PS1). Adenotonsillectomy in children with OSA further resulted in significant reductions in A3β42 and PS1 levels, suggesting that OSA may accelerate AD-related processes [15]. These studies suggest that the activity of tau and Aβ is altered in OSA and may contribute to the future development of neurodegenerative disorders.

Oxidative stress, as a result of repetitive hypoxia and re-oxygenation during OSA [16,17], leads to the activation of pro-inflammatory cascades [18]. Inflammatory biomarkers such as IL-6 have recently garnered attention for their role in promoting vascular inflammation [19] and contribution to OSA-related cardiovascular morbidity [20,21]. Understanding the association between blood biomarkers of neuronal pathology (tau and Aβ40/42) and those of inflammation (TNFα, IL-6, IL-10, and CRP) in younger patients with OSA could help establish an understanding of the course of these chronic illnesses.

OSA is typically viewed as a disorder associated with middle-aged males, and our previous research has shown that military personnel are diagnosed with OSA at a mean age of 36.7 years [22]. However, instituting appropriate treatment at an earlier age could potentially delay the development of neurodegenerative changes. The purpose of our study was to determine whether peripheral blood levels of tau, Aβ, and other markers of inflammation (IL-6, IL-10, CRP, and TNF-α) are elevated in relatively young patients with OSA. An additional exploratory aim was to determine whether peripheral tau was elevated in proportion to the severity of sleep-disordered breathing (SDB). Determining the biological contributors of OSA-related health risks could lead a better understanding of the pathophysiology of this complex disorder.

2. Materials and methods

2.1. Study design and participants

All 74 participants were active duty military personnel with no prior diagnosis of traumatic brain injury (TBI) and/or were screened negative for TBI on the Warrior Administered Retrospective Casualty Assessment Tool [24]. Participants underwent a clinical sleep medicine evaluation, which included a neurological examination with mental status assessment [23]. All participants had no signs or symptoms of neurodegenerative disease as determined from a clinical interview, and a medical data review of their records was performed to exclude individuals with a diagnosis suggestive of cognitive impairments.

All patients in the study underwent an attended in-laboratory diagnostic polysomnogram (PSG) using standardized techniques (Polysmith 5.0, Neurotronics, Gainesville Florida) with 16 channels including electrooculogram, electroencephaologram, electrocardiogram, electromyogram (submental and bilateral tibial) air flow measurements using both oronasal thermal sensors and nasal air pressure transducers, tracheal sounds using microphone, rib cage and abdominal movement by inductance plethysmograhpy using thoracoabdominal belts, and continuous pulse oximetry. Note that no patients in the study underwent a split-night PSG. Participants were classified as having moderate-severe OSA (n = 28) if the apnea-hypopnea index (AHI) was ≥15/h and mild OSA (n = 21) if the AHI was ≥5/h and <15/h. For PSGs prior to July 2013, hypopneas were scored using the American Academy of Sleep Medicine (AASM) alternate scoring criteria [25], and after August 2013, hypopneas were scored in accordance with the AASM revised scoring criteria [26]. Healthy controls had an AHI < 5/h and no clinically significant sleep disorders. Blood samples were processed following standard protocols within 30 min of the blood draw. Biometric parameters of age, gender, race, and BMI were obtained from each participant. The height and weight of each participant were measured during their evaluation, which was used to calculate their BMI. The presence or absence of the diagnosis of hypertension was ascertained from the patient's medical record.

The Neurobehavioral Symptom Inventory (NSI) is a 22-item self-report questionnaire. The tool was administered by trained research assistants to measure neurological symptom severity and rates the presence/severity of each symptom on a five-point scale (none, mild, moderate, severe, and very severe). The NSI has a high internal consistency (total alpha = 0.95; subscale alpha = 0.88–0.92) and reliability (r = 0.88–0.93) [27]. Additionally, the Quick Inventory of Depressive Symptomatology (QIDS) measured total symptoms of depression. QIDS scores range from 0 to 27 [28]. This study was approved by the Madigan Army Medical Center Institutional Review Board.

2.1.1. Biochemical procedures

Blood was collected between the hours of 9 am and 12 pm. There were no differences within the groups for the time of blood draw. Blood was then processed within 60 min and was frozen at −80 °C until batch assays were undertaken. Total tau, IL-6, TNFα, IL-10, Aβ40, and Aβ42 concentrations from plasma were measured with a digital array technology using single molecule, enzyme-linked immunoarrays (Simoa™) [29]. C-reactive protein (CRP) concentrations were assayed by ELISA from R & D Systems. The limits of detection for tau, IL-6, TNFα, IL-10, Aβ40, and Aβ42 were 0.019, 0.0055, 0.011, 0.0022, 0.196, and 0.045 pg/mL, respectively, a 200- to 1000-fold increase in sensitivity compared to conventional immunoassay analysis methods. The limit of detection for CRP was 0.8–50 ng/mL. The reported coefficients of variation for intra- and inter-plate values were below 10% for all analytes.

2.1.2. Statistical analysis

Statistical analysis was conducted using SPSS Statistics version 23 (IBM Corporation, Chicago, IL). Figures were developed using GraphPad Prism. Clinical variables were compared using analysis of variance (ANOVA) for continuous variables and chi-square (χ^2) for categorical variables. ANOVA was used to compare the three groups. Biomarker concentrations were treated as continuous data, and the Shapiro–Wilk test was used to test the assumption of normality. In ANOVA models, covariates including comorbid depression and insomnia were controlled for using ANCOVA models. Bonferroni corrections adjusted for multiple comparisons and Pearson correlations determined relationships between continuous measures [30].

3. Results

3.1. Demographics and clinical characteristics

The healthy control (n = 24), mild OSA (n = 22), and moderate-severe OSA (n = 28) groups did not differ significantly in age, gender, race, BMI, or number diagnosed with hypertension. The mean age of the participants was 30.9 in the control group and 34.0 and 35.6 in the mild OSA and moderate-severe OSA groups, respectively. The moderate-severe OSA group had the highest arousal index (mean score 26.34) and the lowest oxygen nadir of 82.48% compared to healthy controls and patients with mild OSA (Table 1).

Table 1
Demographic and clinical characteristics of participants.

	Control (n = 24)	Mild OSA (n = 22)	Moderate-Severe OSA (n = 28)	Significance
Demographics and clinical characteristics				
Age, mean ± SD	30.9 ± 7.77	34.0 ± 8.19	35.6 ± 7.77	$F_{2,66} = 0.126$, p = 0.882
Gender, male (%)	22 (91.7%)	21 (95.5%)	28 (100%)	$X^2 = 2.327$, p = 0.312
Race, no. (%)				$X^2 = 11.274$, p = 0.506
White	14 (58.3%)	16 (72.7%)	15 (53.6%)	
Native American	0 (0.0%)	0 (0.0%)	2 (7.1%)	
Asian	1 (4.2%)	1 (4.5%)	0 (0.0%)	
Black	4 (16.7%)	2 (9.1%)	4 (14.3%)	
Native Hawaiian/Pacific Islander	3 (12.5%)	0 (0.0%)	2 (7.1%)	
Other/Unknown	0 (0.0%)	1 (4.5%)	3 (10.7%)	
Mixed race	1 (4.2%)	1 (4.5%)	1 (3.6%)	
BMI, mean ± SD	28.6 ± 3.81	30.5 ± 4.80	31.1 ± 3.75	$F_{2,68} = 2.272$, p = 0.111
NSI scores, mean (SD)	29.37 (18.55)	27.89 (10.85)	32.67 (14.64)	$F_{2,62} = 2.83$, p > 0.05
QIDS score for depression, mean (SD)	9.54 (5.18)	8.78 (4.17)	10.01 (4.00)	$F_{2,71} = 2.54$, p > 0.05
Self-reported measures				
Epworth Sleepiness Scale, mean ± SD	10.20 ± 4.72	12.35 ± 4.32	12.52 ± 4.72	$F_{2,63} = 1.279$, p = 0.285
Pittsburgh sleep quality index, mean ± SD	5.29 ± 2.14	5.76 ± 2.78	7.32 ± 4.73	$F_{2,67} = 2.472$, p = 0.092
PSG variables				
Sleep onset latency, min	7.88 ± 6.0	9.9 ± 7.9	7.5 ± 9.0	$F_{2,67} = 0.650$, p = 0.526
Rapid eye movement latency, min	18.92 ± 4.5	20.28 ± 5.6	17.7 ± 5.9	$F_{2,67} = 0.608$, p = 0.547
Total sleep time, min	415.08 ± 49.4	419.02 ± 49.6	392.49 ± 72.3	$F_{2,67} = 1.454$, p = 0.241
Sleep efficiency, %	92.68 ± 5.4	92.63 ± 5.5	89.83 ± 7.3	$F_{2,67} = 1.725$, p = 0.186
Stage N1, %	8.85 ± 5.0	7.08 ± 2.4	14.13 ± 9.9	$F_{2,67} = 7.083$, p = 0.002
Stage N2, %	42.80 ± 10.9	43.59 ± 9.3	40.71 ± 12.1	$F_{2,67} = 0.467$, p = 0.629
Stage N3, %	25.91 ± 15.7	26.37 ± 9.7	19.53 ± 13.6	$F_{2,67} = 2.124$, p = 0.127
Stage REM, %	18.92 ± 4.5	20.28 ± 5.6	17.67 ± 5.9	$F_{2,67} = 0.608$, p = 0.547
Wakefulness after sleep onset, min	30.23 ± 22.2	29.80 ± 23.9	40.88 ± 32.1	$F_{2,61} = 1.230$, p = 0.299
AI	13.22 ± 6.4	15.47 ± 6.7	26.34 ± 21.7	$F_{2,67} = 5.639$, p = 0.005
AHI	2.12 ± 1.3	8.56 ± 2.5	26.09 ± 21.3	$F_{2,67} = 20.358$, p = 0.000
Oxygen saturation nadir, %	90.00 ± 3.7	86.38 ± 5.4	82.48 ± 7.4	$F_{2,67} = 9.528$, p = 0.000

Note: SD, standard deviation; BMI, body mass index; NSI, Neurobehavioral Symptom Inventory; QIDS, Quick Inventory of Depressive Symptomatology; PSG, polysomnography; REM, rapid eye movement; AI, arousal index; AHI, apnea-hypopnea index.

3.1.1. Proteomic biomarker concentrations

We observed significant differences between the three groups in concentrations of tau ($F_{2,70} = 12.734$, p = 0.000) and IL-6 ($F_{2,70} = 6.844$, p = 0.002). Patients with severe OSA had higher mean tau and IL-6 concentrations (tau: 5.39 ± 2.57 pg/mL; IL-6: 2.93 ± 1.74 pg/mL) than patients with mild OSA (tau: 2.95 ± 2.02 pg/mL; IL-6: 1.74 ± 0.71 pg/mL) and controls (tau: 2.48 ± 1.94 pg/mL; IL-6: 1.72 ± 1.21 pg/mL) (Fig. 1), and these differences remained significant even when BMI was controlled for. Moreover, we independently included covariates in these models, which may be linked to these findings, including demographics (age, race, and gender) and clinical variables (total sleep time, BMI, and hypertension); yet none of these variables changed the significance of the findings.

There were no significant differences found in the other biomarker proteins, ie, TNFα, IL-10, Aβ40, Aβ42, and CRP (data not shown, p > 0.05 for all). Increased tau concentrations were correlated with higher AHI (r = 0.342, p = 0.004) (Fig. 2), and maximum desaturation (0.293, p = 0.02) (data not shown) in the OSA groups. No other biomarker was significantly related to AHI or any of the other PSG sleep measures (p > 0.10 for all).

4. Discussion

Our results show that relatively young patients with moderate-severe OSA have elevated concentrations of tau and IL-6 in peripheral blood samples, compared to patients with mild OSA and healthy controls. Additionally, we report that peripheral tau

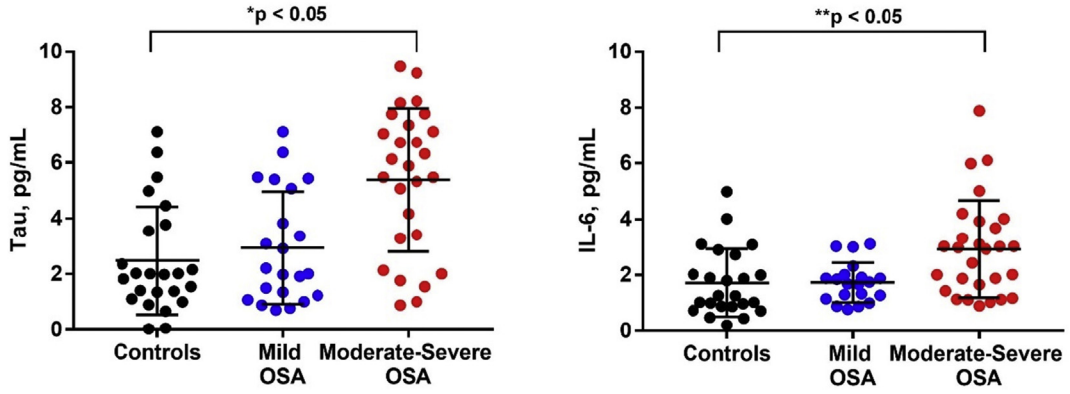

Fig. 1. Comparison of total peripheral tau and IL-6 concentrations between controls and patients with mild and moderate-severe OSA. p-values were calculated using an ANOVA, with a Bonferroni post hoc test.

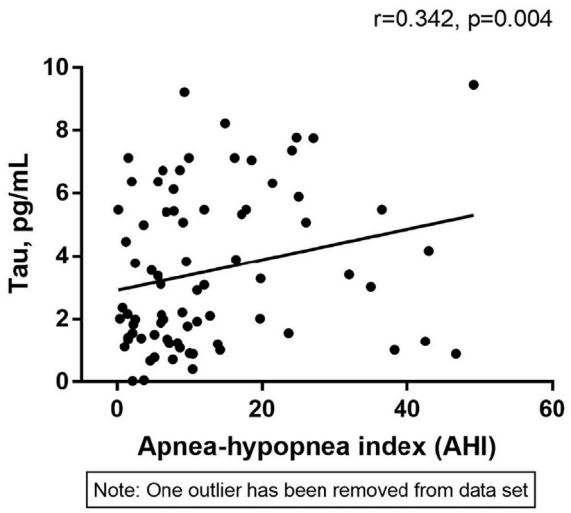

Fig. 2. Significant positive correlation between tau concentrations (pg/mL) and AHI ($r = 0.342$, $p = 0.004$) in participants with OSA (mild and moderate-severe). Multiple comparisons were corrected by Bonferroni post hoc test.

concentrations are correlated with AHI, suggesting that this biomarker may be associated with OSA severity. Given that our sample of young patients did not have comorbidities, the most likely etiology of these findings may be attributed to OSA. Our findings are based on a study in elderly patients showing that higher CSF total tau levels are associated with OSA and cognitive impairments [14]. However, they do not support findings linking Aβ to OSA [13,14]. In contrast to these prior studies, we employed a more sensitive assay detection method, Simoa™, which uses single molecule counting technology, compared to traditional ELISA methods, allowing for the use of plasma instead of CSF [31], which increases the clinical applicability of the study findings.

Developing the temporal relationship between tau and OSA is important as tau-related neuronal degeneration, according to our findings, and may begin early in the course of this chronic illness. In a recent study, even one week of disturbed sleep in a middle-aged cohort was related to elevations in Aβ40 and worse sleep quality associated with increased CSF tau, suggesting an association between sleep disruption and the risk for neurodegenerative disease later in life [32]. There is some evidence of the impact of age on the relationship between SDB and tau. Specifically, moderate-severe SDB was associated with greater tau and p-tau in elderly patients (mean age = 68.95 years) compared to those with mild SBD and healthy controls, indicating that SDB may shape tau pathology and contribute to AD-associated cognitive impairments and dementia [33]. In OSA, reductions in the volume of the hippocampus, caudate, and cortical gray matter (GM) relate to poor performance on neurocognitive tasks [34]. Furthermore, a PET study of patients with OSA revealed significant cerebral changes, with GM reductions and decreases in brain metabolism, compared to healthy controls, suggesting that OSA contributes to lasting neuronal changes [35]. Together these studies suggest that tau relates to neuronal impairment in OSA; however, additional long-term studies in representative samples are needed to confirm these associations. Developing biomarkers related to OSA and neuronal changes is important as there is a demonstrable association between neurodegeneration and OSA, but temporal relationships remain elusive [36]. Our study builds on these findings by reporting increases in peripheral tau in a cohort of younger patients than previously studied, thereby providing key insights into the potential inflammatory and neurodegenerative processes that may begin early in the course of this chronic disease.

We also report that IL-6 is elevated in this young cohort with moderate-severe OSA, supporting previous findings in older patient groups [37–41]. As hypertension was infrequent in these patients, the most likely etiology for increased IL-6 was SDB. These peripheral elevations likely result from oxygen desaturations that cause diffuse hypoxia-related injury, which aggravates existing inflammatory responses or induces new responses in damaged tissue [42]. Excessive inflammation is a potential contributing factor to the development of cardiovascular and cerebrovascular complications that patients with OSA are at risk of [43–46].

We observed no differences in Aβ levels between any of the three groups. This contrasts previous preclinical studies that have observed associations between conditions of chronic hypoxia and increased Aβ production [47,48] and observed significant blood elevations of Aβ in patients with OSA [13,15]. Taken together, our findings suggest that Aβ pathological development may be at subclinical levels of detection in these young individuals. Moreover, Aβ levels may be peripherally undetectable early in the course of this chronic disorder because of sequestration of Aβ directly in the central nervous system. Thus, further studies are needed to further elucidate the time course of this critical protein to mitigate the development of cognitive deficits.

Clinically accessible biomarkers such as those reported here are necessary to improve the timely diagnosis of OSA-associated morbidity and to possibly ameliorate the risk of neurological damage and cognitive deficits. While it has been recently observed that peripheral tau concentrations are associated with cognitive declines [49,50], undoubtedly, CSF analysis remains the most sensitive assay method for the prediction of cognitive deficits because the CSF is in direct contact with the brain [51]. However, peripheral blood measurement remains a more clinically accessible and feasible method for biomarker detection. There is a need for future longitudinal studies to examine the temporal relationship of these biomarkers, and their associations with cognitive impairments to accurately characterize the progression of OSA. Findings from future studies may lead to the identification of patients with OSA at high risk for cognitive impairment and neuropathology and identify novel targets to prevent long-term morbidity.

Our study has limitations that merit discussion. As the time period for recruitment of subjects extended over a revision in scoring criteria by the AASM, two different scoring methods were used. The hypopnea scoring criteria from 2012 and the alternative criteria for scoring hypopneas from 2007 differ on the decrease in the nasal pressure signal amplitude, from 30% of baseline in 2012 to 50% in 2007. Thus, patients in the cohort prior to the implementation of the 2012 criteria may have had a lower AHI on the basis of this change. Our analysis of the biomarkers from the patients in the two time periods (specifically, those scored using the 2007 alternate versus the 2012 AASM criteria) did not show any difference; thus, the scoring methodology change likely did not affect our results for the biomarkers tau or IL-6. Hypoxia is related to biomarkers of AD [33], but in our analysis, we did not evaluate other indices of hypoxia, ie, oxygen desaturation index (ODI). While patients with severe OSA likely have a higher ODI, we cannot make an assessment about this parameter, which could have contributed to our findings. Additionally, while no participant had signs or symptoms of neurodegenerative disease on the basis of clinical evaluation, formal neuropsychological testing was not performed. The patients in our cohort have sleepiness, which is not necessarily typical of all patients with OSA, as most military personnel sleep 6 h per night. The effects of insufficient sleep may in part contribute to our findings, but to date, no study has determined whether tau is elevated solely because of insufficient sleep in humans [32,52–54]. Furthermore, insufficient sleep related to military service would equally affect patients in the control group and the sleep apnea

groups. Nevertheless, his study suggests that tau and IL-6 provide insights into patients who may be at risk for irreversible neuronal pathology due to OSA, helping to focus clinical efforts on those patients who require definitive treatment for this disorder.

5. Conclusion

OSA is the most prevalent type of SDB and is characterized by recurrent cycles of upper airway obstruction, hypoxia, and sleep fragmentation. We found elevated levels of tau and IL-6 in a relatively young cohort with moderate-severe OSA. These findings suggest that inflammation and neuronal damage may begin early in the course of this chronic illness and that this degree of SDB may contribute to the development of neurodegenerative disorders. This knowledge could determine which patients require early definitive therapy to potentially mitigate and prevent irreversible neuronal damage.

Acknowledgments

The opinions and assertions in this manuscript are those of the authors and do not necessarily reflect the official policy or position of Brooke Army Medical Center, the U.S. Army Medical Department, the U.S. Army Office of the Surgeon General, the Department of the Air Force, the Department of the Army, the Department of Defense, the U.S. Government, or the Center for Neuroscience and Regenerative Medicine. We thank the military personnel who participated in this study.

Conflict of interest

No author has any conflicts of interest to disclose. This work was supported by the Center for Neuroscience and Regenerative Medicine (Grant 60855) and the National Institutes of Health Intramural Research Program.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2017.11.1121.

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