Sleep Medicine 15 (2014) 27–32

Contents lists available at ScienceDirect

Sleep Medicine

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

Original Article

Obstructive sleep apnea and neurocognitive performance: the role of cortisol

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ARTICLE INFO

Article history:
Received 28 March 2013
Received in revised form 7 August 2013
Accepted 23 August 2013
Available online 31 October 2013

Keywords:
Obstructive sleep apnea
Sleep
Neurocognitive function
Memory
Cortisol
Hypothalamic–pituitary–adrenal axis

ABSTRACT

Background: Obstructive sleep apnea (OSA) is a prevalent disorder with multiple consequences including negative effects on neurocognitive function. Several domains of cognitive function are impaired in OSA patients, but the mechanisms through which this sleep disorder results in impairment are not clear. Given the well-known effects of cortisol on cognitive function, in particular memory, the dysregulating effects of OSA on cortisol levels are hypothesized as a potential pathway leading to cognitive impairment.
Methods: Fifty-five participants with OSA (mean apnea-hypopnea index [AHI], 30.3) were assessed over 2 days. Over a 24-h period, blood samples were collected every 2 h to examine cortisol levels. The following night, sleep was monitored with polysomnography (PSG). Participants were given a battery of neurocognitive tests, which assessed seven cognitive domains.
Results: OSA severity assessed by oxygen desaturation index (ODI) was associated with 24-h cortisol levels. AHI, ODI, and nighttime cortisol levels were associated with global deficit scores (GDS) in cognitive functioning, particularly in domains of learning, memory, and working memory ($P < .05$ for all). Hierarchical linear regression analysis revealed that nighttime cortisol accounted for 9–16% of variance in learning ($P = .018$), memory ($P = .003$), and working memory ($P = .016$) domains, though apnea severity did not significantly predict any additional variance.
Conclusions: In our sample of patients with OSA, nocturnal cortisol levels were associated with neuropsychologic functioning above and beyond the influence of covariates and apnea severity. These findings suggest that OSA-related alterations in cortisol activity may partially explain the pathophysiology of neuropsychologic impairments in sleep apnea.

1. Introduction

Obstructive sleep apnea (OSA) is a sleep disorder involving repeated episodes of complete or partial obstruction of the upper airway, which cause transient cessations of breathing during sleep. These breathing disruptions cause intermittent hypoxia and sleep disturbances which are associated with daytime sleepiness and fatigue [1]. OSA also has been demonstrated to have negative effects on cognitive functioning, which add to the public health risks for the disease [2]. The neurobehavioral consequences of OSA extend to functional impairments, such as impaired driving, increased risk for accidents, and decreased quality of life [3,4]. Numerous studies have examined the effects of OSA on the cognitive abilities underlying these neurobehavioral consequences. Impairments in memory, vigilance, psychomotor performance, and executive function all have been reported in OSA patients, but the presence and degree of impairments is inconsistent between studies [5–12]. A recent meta-analysis [2] of systematic reviews found support for impairments in attention or vigilance, delayed verbal and visual long-term memory, visuospatial or constructional abilities, and executive function. Further, neuroimaging studies have reported structural changes in specific brain regions associated with cognitive function, and the loss of hippocampal volumes in OSA patients is consistently reported [13].

Associations between cognitive function tests and magnetic resonance imaging findings have been reported for verbal memory and information processing [14], as well as for verbal memory and executive function [15].

The mechanisms by which OSA results in neurocognitive dysfunction are not entirely clear for several reasons. The comorbidities that accompany OSA (e.g., hypertension) are associated with neural injury, making it important to control for confounding associations of OSA to neurocognitive impairment (see [1] for review).

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http://dx.doi.org/10.1016/j.sleep.2013.08.789

In addition, the variety of tests used to assess neurocognitive function along with the varied sample characteristics are vast, which limit the possibilities for comparing the reported cognitive sequelae of OSA [16]. Further, individual differences in the severity of sleep disturbances also may add variability to the pattern of neurocognitive deficits observed in patients with OSA, with greater deficits found in more severe OSA, particularly in the case of executive function [17,18].

The neurochemical, vascular, and structural changes accompanying hypoxemia and sleep fragmentation have been implicated in the adverse effect of OSA on cognitive functioning (see [16] for review). One potential pathway of interest might be dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis. The primary human product of the HPA axis is cortisol, a hormone that evidences a strong diurnal rhythm. The fluctuation of cortisol throughout the night is intricately related to sleep, and thus it has been proposed as an important mechanism through which sleep disorders manifest some of their physiologic changes. Further, both the hippocampus and amygdala, which are strongly involved in memory processes, express a high density of corticosteroid receptors [19]. Given the association between cortisol and cognitive function and the association between OSA and cognitive dysfunction, the role that cortisol may play in cognitive dysfunction in OSA is worthy of investigation.

The literature linking OSA and HPA function is mixed, and few studies have found differences in cortisol levels between OSA and healthy patients [20]. However, many studies are limited by the assessment of cortisol levels at a single time point [21,22]. Those investigations that have reported differences used extensive circadian sampling [23]; additionally, elevated cortisol levels appeared to be corrected after treatment with continuous positive airway pressure (CPAP) [23–25]. Cortisol levels, especially during the night, might be an important factor in the association between OSA and neurocognitive functioning. In our study, we examined the 24-h cortisol profile in 55 patients with OSA and its association with performance in cognitive function tests. It was hypothesized that increased OSA severity would be associated with both decreased cognitive performance and elevated cortisol levels.

2. Methods

2.1. Participants

As part of a larger study (National Institutes of Health HL44915) examining the pathophysiology of the sympathetic nervous system in patients with OSA [26], participants with known or suspected OSA who had not received previous OSA treatment were recruited via advertisements, word of mouth referral, and referral from local medical practices in the San Diego area. Fifty-five participants with OSA were included (age range, 29–65 y). Potential participants were excluded if they (1) had a history of a major medical illness, with the exception of OSA and hypertension; (2) had current psychiatric diagnoses including alcohol or drug abuse; or (3) were receiving psychotropic medications. Two patients who were taking hypertensive medication were slowly tapered off their medications for 3 weeks prior to participation. In both cases, blood pressure (BP) remained within the inclusion range (<170/105 mmHg), and thus the patients were retained in the sample. The full details of the procedure are described elsewhere [26]. The project and all procedures were approved by the University of California, San Diego Human Subjects Committee.

2.2. Procedure

Written informed consent was obtained from all participants before participation in the study. Participants were admitted to the University of California, San Diego, General Clinical Research Center Gillin Laboratory of Sleep and Chronobiology for two nights. The participants were prepared for standard polysomnography (PSG) on both nights; however, the recordings were discarded from the first night due to the possibility of first-night effects on sleep metrics. A venous catheter was inserted at 5:00 pm. Starting at 6:00 pm, a blood sample was collected every 2 h for 24 h. Blood samples were collected in ethylenediaminetetraacetic acid, placed on ice, and spun in a refrigerated centrifuge; the plasma was then stored at −80 °C until assayed. Plasma cortisol was determined using commercial sandwich enzyme-linked immunosorbent assays (Parameter assay; R&D Systems, Minneapolis, MN, USA).

Starting at 8:00 pm the following evening on completion of the 24-h blood sampling, participants were prepared for PSG. The PSG setup began at 9:00 pm and lights-off time occurred between 10:00 pm and midnight. Parameters measured during PSG included electroencephalography, electrocardiography, electrooculography, chin and tibialis anterior electromyography, pulse oximetry, nasal-oral airflow by nasal cannula pressure transducer and thermistor, and thoracic and abdominal respiratory effort recorded on a Grass Heritage digital PSG (Model PSG36-2, Astro-Med, Inc, West Warwick, RI). The next morning, participants were awakened at 6:00 am and PSG recording equipment was removed. Experienced PSG technicians scored PSG sleep records according to the Rechtschaffen and Kales criteria [27]. OSA can be quantified in several ways; each of these indices captures a slightly different aspect of breathing cessation. The most commonly used assessments are recording the number of apneas and hypopneas, oxygen desaturation events, and total sleep time (TST). Apneas were defined as decrements in airflow of $\geqslant$90% from baseline lasting for $\geqslant$10 s. Hypopneas were defined as decrements in airflow of $\geqslant$50% but <90% from baseline lasting for $\geqslant$10 s regardless of the presence or absence of associated desaturation or arousal. Significant transient oxyhemoglobin desaturations were defined as transient drops in oxyhemoglobin saturation by $\geqslant$3% from baseline lasting for >10 s but <3 min. The oxygen desaturation index (ODI) was calculated as the number of transient oxygen desaturations per hour of sleep. TST was computed, and the numbers of apneas and hypopneas per hour of sleep were calculated to obtain the apnea–hypopnea index (AHI). Different criteria for OSA diagnosis exist; in our study, we used a cutoff of AHI $\geqslant$5 events per hour for diagnosis of OSA and inclusion into the study, which is in accordance with the criteria of the American Academy of Sleep Medicine [28]. The mean AHI for the included patients was 30.3 events per hour, with an interquartile range of 30.2 events per hour, thus showing moderate to severe OSA.

2.3. Neuropsychologic battery

Participants were given the following fixed battery, which assessed seven cognitive domains: (1) Wechsler Adult Intelligence Scale-Revised [29]; (2) Digit Symbol, Digit Span, Letter-Number Sequencing Test, Symbol Search Test; (3) Brief Visuospatial Memory Test-Revised (BVMT) [30]; (4) Hopkins Verbal Learning Test-Revised (HVLT) [31]; (5) Trail Making Test parts A and B [32]; (6) Digit Vigilance Test [33]; (7) Stroop Color-Word Test [34]; and (8) Word Fluency Test [35]. These tests produced 15 subscale scores per participant and assessed the following cognitive domains: (1) processing speed (Digit Symbol Test, Symbol Search Test, Digit Vigilance Test, Trail Making Test part A, Stroop Color-Word Test); (2) working memory (Letter-Number Sequencing Test, Digit Span test, Digit Vigilance Test); (3) executive functions (Trail Making Test part B, Digit Symbol Test, Symbol Search Test, Letter-Number Sequencing Test, Stroop Color-Word Test); (4) attention (Digit Vigilance Test); (5) learning (HVLT-total, BVMT-total), and (6) memory (HVLT-recall, BVMT-recall).