

# Relationship between inflammation and cognitive function in obstructive sleep apnea

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## Abstract

**Objectives** Obstructive sleep apnea (OSA) can have adverse effects on cognitive functioning, mood, and cardiovascular functioning. OSA brings with it disturbances in sleep architecture, oxygenation, sympathetic nervous system function, and inflammatory processes. It is not clear which of these mechanisms is linked to the decrease in cognitive functioning. This study examined the effect of inflammatory parameters on cognitive dysfunction.

**Materials and methods** Thirty-nine patients with untreated sleep apnea were evaluated by polysomnography and completed a battery of neuropsychological tests. After the first night of evaluation in the sleep laboratory, blood samples were taken for analysis of interleukin 6, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and soluble TNF receptor 1 (sTNF-R1).

**Results** sTNF-R1 significantly correlated with cognitive dysfunction. In hierarchical linear regression analysis,

measures of obstructive sleep apnea severity explained 5.5% of the variance in cognitive dysfunction (n.s.). After including sTNF-R1, percentage of variance explained by the full model increased more than threefold to 19.6% ( $F=2.84$ ,  $df=3, 36$ ,  $p=0.05$ ). Only sTNF-R1 had a significant individual relationship with cognitive dysfunction ( $\beta=0.376$   $t=2.48$ ,  $p=0.02$ ).

**Conclusions** sTNF-R1 as a marker of chronic inflammation may be associated with diminished neuropsychological functioning in patients with OSA.

**Keywords** Obstructive sleep apnea · Cognitive dysfunction · Cytokine · IL-6 · TNF- $\alpha$  · sTNF-R1

## Introduction

Obstructive sleep apnea (OSA) is characterized by chronically fragmented sleep and recurrent transient hypoxemia. Common sequelae of OSA include cardiovascular risk, excessive daytime sleepiness, mood disorder, and neuropsychological dysfunction [1, 2].

Obstructive sleep apnea can have a negative impact on cognitive functioning but the mechanisms responsible for this dysfunction have not been elucidated. A recent review analyzed patterns of neuropsychological deficits in OSA patients [3]. Attention–vigilance, executive functioning, and memory were impaired in at least 60% of the studies reviewed, and visuoconstruction and psychomotor functioning impairments were noted in 80% of the studies. A substantial impairment of vigilance and executive functioning in OSA patients was also found in a second meta-analysis [4]. In the latter review, general intelligence and verbal ability were unaffected by OSA and apnea's effects on visual and motor skills and memory were inconsistent.

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It is unclear whether the disturbances in sleep architecture and/or the drops in oxygenation are the primary causes of cognitive problems in OSA. In a review of nine placebo-controlled studies that evaluated cognitive functioning pretreatment and posttreatment, continuous positive airway pressure (CPAP) treatment was only rarely superior to placebo [5]. These studies were also inconclusive regarding the effects of treatment on specific cognitive domains. CPAP's beneficial effects were inconsistent for sustained attention, memory, executive functioning, and psychomotor function in the above-mentioned meta-analysis [3].

Similarly, associations between apnea severity and cognitive dysfunction appear inconsistent. Although most studies have found an association between apnea severity variables and at least one domain of cognitive performance, only global cognitive functioning and attention–vigilance have been consistently related to apnea severity. In our placebo-controlled studies of CPAP treatment of OSA patients, we observed global cognitive improvement in one study [6] but not in another [7]. However, in both studies, vigilance was the only specific domain observed to improve in association with CPAP treatment [6, 7].

A possible mechanism responsible for cognitive dysfunction in the OSA patient involves inflammatory cytokines. There is a significant association between peripheral inflammatory markers and cognitive performance. Peripheral proinflammatory cytokines such as interleukin-1 (IL-1) and IL-6 can affect central nervous system functioning by penetrating the blood–brain barrier directly through active transport mechanisms or indirectly through activation of the afferent vagus nerve [8–10]. Also, chronic elevation of proinflammatory cytokine levels can promote neurodegeneration and such chronic elevation is related to impairment of cognitive functioning [11]. Patients with diseases of cognitive function such as Alzheimer's disease or multi-infarct dementia show altered peripheral production of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ; [12]). Poorer cognitive function in older, reasonably healthy African–Americans and Caucasian–Americans has also been associated with higher peripheral levels of IL-6, and higher IL-6 levels may be associated with cognitive decline in the general older population [11, 13, 14]. Thus, cytokine-mediated central inflammatory processes may be very relevant to cognition [15].

These observations on inflammation and cognition are germane to OSA, as numerous studies have reported increased levels of inflammation and inflammatory markers (IL-6, TNF- $\alpha$ , and C-reactive protein) in patients with OSA [16, 17]. The significant elevations of IL-6 and TNF- $\alpha$  are independent of body mass index (BMI) but relate to OSA severity, measured by the apnea–hypopnea index (AHI; [18]). Elevated cytokines, as part of a chronic

inflammatory process, have been suggested as a possible mechanism for the increased cardiovascular risk associated with OSA [19].

In an attempt to answer whether cytokines play an important role in cognitive functioning of OSA patients, we compared the relative importance of markers of OSA severity and inflammation vis-à-vis neuropsychological functioning in OSA patients.

## Materials and methods

### Participants

People with a history suggestive of OSA were recruited by advertisement and word of mouth referral or were referred by local sleep centers, medical practitioners in the San Diego area, and by previous participants in our laboratory's studies. We limited enrollment to subjects in the age range of 30 to 65 years and with no more than 200% of ideal body weight as determined by Metropolitan Life Foundation height and weight tables [20].

Because we are trying to investigate specific OSA-related mechanisms, we used stringent exclusion criteria to minimize other sources of cognitive disturbance. Patients were excluded if they had a history of heart, liver, or renal disease, diabetes, psychosis, narcolepsy, current alcohol or drug use disorders, severe asthma, or cerebrovascular disease, or prior diagnosis or treatment of OSA. Pregnancy as well as current prescription medications except antihypertensive medication were additional criteria for exclusion. Patients receiving antihypertensive medication had their treatment tapered slowly in two to three steps depending on the patient's regular dosage. A 3-week drug washout period was observed before studying the patients. Individuals whose blood pressure exceeded 180/110 mmHg were returned to active treatment and were not studied in this protocol.

The project was approved by the University of California, San Diego, Human Subjects Committee and written informed consent was obtained from the subjects prior to participation in the study.

All subjects were screened for OSA using an unattended overnight home sleep recording system study (Stardust; Respironics Inc., Marietta, GA, USA). Subjects with an AHI (number of apneas plus hypopneas per hour of sleep) of at least 15 were admitted to the General Clinical Research Center (GCRC) Gillin Laboratory of Sleep and Chronobiology for three nights.

If the polysomnography recording on the first night confirmed an  $AHI \geq 15$ , subjects were considered to have presumptive OSA and were invited to continue in the study.

None of the subjects had predominant central sleep apnea (defined as  $\geq 50\%$  central respiratory events).

## Measures

### *Sleep recordings*

Sleep was monitored with the Grass Heritage digital polysomnograph (Model PSG36-2, Astro-Med, Inc., West Warwick, RI, USA). Central and occipital electroencephalogram, bilateral electrooculogram, submental and tibialis anterior electromyogram, electrocardiogram, body position, nasal airflow using a nasal cannula–pressure transducer, and naso-oral airflow using a thermistor were assessed. Respiratory effort was measured using chest and abdominal piezoelectric belts. Oxyhemoglobin saturation ( $S_aO_2$ ) was monitored using a pulse oximeter (Biox 3740; Ohmeda: Louisville, CO, USA) and scored with Profox Software (Profox; Escondido, CA, USA). Sleep records were manually scored according to the criteria of Rechtschaffen and Kales [21]. AHI was calculated as the average of the total number of apneas (decrements in airflow of  $\geq 90\%$  from baseline for  $\geq 10$  s) and hypopneas (decrements in airflow of  $\geq 50\%$  but  $< 90\%$  from baseline for  $\geq 10$  s) experienced per hour of sleep [22].

### *Neuropsychological tests*

Subjects were given the following battery at baseline: Wechsler Adult Intelligence Scale-III Digit Symbol, Symbol Search, Digit Span, and Letter–Number Sequencing; Brief Visuospatial Memory Test Revised; Hopkins Verbal Learning Test Revised; Trail Making A/B; Digit Vigilance Test; Stroop Color–Word Test; and Controlled Oral Word Association Test [23–31]. These tests produced 15 raw scores per subject and assessed the following cognitive domains: speed of information processing; attention and working memory; executive functions; verbal learning and memory; visual learning and memory; and verbal fluency. The tests were administered at 1:00 PM by the same research personnel and required approximately 60 min to complete.

### *Psychological assessment*

The Center for Epidemiologic Studies Depression Scale (CESD), a 20-item self-report scale, was used to assess depressive symptoms [32]. Scores  $\geq 16$  on the CESD suggest a diagnosis of dysthymia or major depression [33]. The CESD primarily taps cognitive–affective aspects of depression and has been shown to be useful in chronically ill groups experiencing fatigue (e.g., HIV, cancer), including OSA patients [34–38].

### *Inflammatory markers*

Blood was drawn upon awakening around 6:30 AM the morning after the first night of sleep in the GCRC. Blood was collected in ethylene diamine tetraacetic acid for IL-6, TNF- $\alpha$ , and soluble TNF receptor 1 (sTNF-R1). Early morning blood draw was accomplished before the subjects got out of bed in order to avoid possible effects of major movements on such levels. Plasma was stored at  $-80^\circ\text{C}$  until further assessment was performed. IL-6, TNF- $\alpha$ , and sTNF-R1 levels were assessed by using a high-sensitivity enzyme-linked immunosorbent assay from R&D Systems (Minneapolis, MN, USA). The precision of the assays was as follows: intra-assay variations (CV) for IL-6, TNF- $\alpha$ , and sTNF-R1 were 2.0%, 8.0%, and 3.9%; interassay variations (CV) were 3.5%, 16.3%, and 4.8%, respectively. Sensitivity values for IL-6, TNF- $\alpha$ , and sTNF-R1 were  $< 0.70$  pg/ml,  $< 0.18$  pg/ml, and  $< 0.52$  pg/ml.

### *Data analyses*

TNF- $\alpha$  data were log-transformed to approximate a normal distribution. Raw scores on the neuropsychological tests were converted to demographically converted *T* scores (controlling for age, education, gender, and ethnicity, as appropriate). Higher *T* scores indicate better performance. A deficit score was computed for each of the 15 individual test scores, according to the convention below; *T* scores were collapsed into groups from 0 to 5. The average of those scores is the global deficit score (GDS; [39]). A *T* score  $\geq 40$  (normal) yields a deficit score of 0;  $\geq 35$  and  $< 40$  (mildly impaired) yields a deficit score of 1;  $\geq 30$  and  $< 35$  (mild to moderate impairment) yields a deficit score of 2;  $\geq 25$  and  $< 30$  (moderate impairment) is scored as a 3;  $\geq 20$  and  $< 25$  (moderate to severe impairment) is scored as a 4; and  $< 20$  (severe impairment) is scored as a 5.

Pearson correlations were used to determine bivariate associations among the baseline GDS, BMI, CESD, OSA severity variables (AHI,  $\%O_2 < 90$ ), and markers of inflammation (IL-6, TNF- $\alpha$ , sTNF-R1). Of the inflammatory markers, only sTNF-R1 showed a significant bivariate relationship with GDS; therefore, it was the only inflammatory marker included in the subsequent hierarchical analysis. Hierarchical linear regression analysis was used to model associations for GDS vs. OSA severity variables and sTNF-R1. While the OSA severity variables did not show significant bivariate relationships with GDS, we decided to take a conservative approach and include them in the hierarchical model to ensure that variance in cognitive functioning due to OSA severity was controlled.

Statistical analyses were performed using SPSS statistical software (SPSS for Windows 12.0: SPSS Inc.;

Chicago, IL, USA). Observations were considered significant at  $p < 0.05$ .

## Results

### Demographics

Characteristics of patients are presented in Table 1. The majority of participants were male (85%) and Caucasian (72%). Subjects were middle aged (mean age  $47.6 \pm 1.6$  years) and mildly obese (BMI  $31.1 \pm 0.9$  kg/m<sup>2</sup>). On average, participants had severe OSA (mean AHI  $63.9 \pm 4.9$ ). Oxyhemoglobin desaturation during the night was mild with the mean of time spent at an oxygen saturation below 90% ( $\%O_2 < 90$ ) at  $7 \pm 2.1\%$  of total time in bed.

### Pearson's correlations

We first examined correlations between OSA severity variables (AHI and  $\%O_2 < 90$ ) and the inflammatory markers. We observed a trend toward a positive association between AHI and sTNF-R1 ( $r = 0.31$ ,  $p = 0.071$ ). Correlations for GDS vs. patient characteristics, CESD, OSA severity variables, and inflammatory markers are shown in

**Table 1** Patient characteristics prior to treatment ( $\pm$ standard error of the mean;  $n = 39$ )

Patients characteristics prior to treatment	
Age (years)	47.6 $\pm$ 1.6
Gender (%)	
Male	85
Female	15
Ethnicity (%)	
Caucasian	72
African–American	10
Hispanic	5
Asian	8
Other	5
Education (%)	
Graduate school	10
College graduate	39
Partial college	28
High school graduate	20
Partial high school	3
BMI (kg/m <sup>2</sup> )	31.1 $\pm$ 0.9
AHI	63.9 $\pm$ 4.9
$\%O_2 < 90$	7 $\pm$ 2.1
IL-6 (pg/ml)	3.6 $\pm$ 0.4
TNF- $\alpha$ (pg/ml)	1.7 $\pm$ 0.2
sTNF-R1 (pg/ml)	908.3 $\pm$ 34.2
GDS	0.3 $\pm$ 0.06

BMI Body mass index, AHI apnea–hypopnea index,  $\%O_2 < 90$  oxygen saturation below 90%

Table 2. sTNF-R1 was the only variable significantly correlated with GDS ( $r = 0.387$ ,  $p = 0.015$ ).

### Hierarchical linear regression analysis

Table 3 shows the results of the hierarchical linear regression analysis using GDS as the dependent variable and OSA severity variables and sTNF-R1 as the independent variables. In step 1, AHI and  $\%O_2 < 90$  together explained 5.5% of the variance in GDS. Even though the OSA severity variables were nonsignificant in the bivariate correlation, we took a conservative approach by forcing AHI and  $\%O_2 < 90$  together into the first step of a hierarchical regression analysis, to see if sTNF-R1 would subsequently contribute significantly to the prediction of neuropsychological functioning. In step 2, after including sTNF-R1 using forced entry, the percentage of variance in GDS explained by the full model increased more than threefold to 19.6% ( $F = 2.84$ ,  $df = 3, 36$ ,  $p = 0.05$ ). Only sTNF-R1 was a significant, individual predictor in the model ( $\beta = 0.376$ ,  $t = 2.48$ ,  $p = 0.02$ ).

## Discussion

This study examined the relationship between cognitive functioning, measures of sleep apnea severity, mood, and inflammatory markers in a sample of patients with severe untreated OSA. We observed a trend toward a positive association between OSA severity and inflammation. While the lack of a stronger association is likely due to limited statistical power, this trend nonetheless is in agreement with OSA inflammation links reported in the literature. [16, 17] The results of multivariate analyses suggest that sTNF-R1 was the most important predictor of cognitive status, accounting for almost 20% of variance in GDS. In other words, inflammation (as measured by sTNF-R1) explained three times as much variance of the GDS as did OSA severity (AHI and  $\%O_2 < 90$ ).

Receptors for TNF- $\alpha$  occur physiologically as an inhibitor and modulator of TNF- $\alpha$  [40]. TNF receptor levels occur in much higher concentrations in the circulation than TNF- $\alpha$ , making assessment more reliable [41]. The difference in findings regarding TNF-R1 and TNF- $\alpha$  may also represent assay sensitivity, which is quite limited for TNF- $\alpha$ . There are different forms, sTNF-R1 and sTNF-R2 (also called sTNF-R p55 and sTNF-R p75), and both are shed into the circulation by various cell types such as activated lymphocytes, neutrophils, epithelial cells, and tumor cells. The receptors compete with cellular TNF receptors for TNF- $\alpha$ , thus changing its bioavailability. After a challenge to the immune system, TNF-R increases rapidly; increases are also found in clinical conditions such



**Table 2** Pearson's correlations: patient characteristics vs. Global Deficit Score ( $n=39$ )

Patient Characteristics	Pearson's $r$	$P$
Age	0.144	0.382
BMI	0.081	0.625
AHI	0.024	0.885
%O <sub>2</sub> <90	0.207	0.206
Mean SaO <sub>2</sub>	-0.169	0.303
CESD	-0.106	0.520
IL-6	0.234	0.170
TNF- $\alpha$	0.009	0.958
sTNF-R1	0.387	0.015

as rheumatoid arthritis and psoriasis [40, 42, 43]. sTNF-R1 shows a fairly consistent 24-h rhythm with peak values in the early morning hours, and sleep deprivation increases their values in healthy subjects [44, 45]. Less is known of the role of sTNF-R1 in OSA patients, but its substrate, TNF- $\alpha$ , shows an altered circadian variability in OSA [46]: OSA patients exhibit increased TNF- $\alpha$  concentrations in the afternoon instead of a normal peak during the night. It might therefore be interesting to study circadian variability of sTNF-R1 in future studies.

The impact of cytokines on cognitive disturbance has been studied during mild stimulation of primary host defense in healthy subjects [47]. In a double-blind crossover study, healthy volunteers were given intravenous injection of endotoxin or saline and neuropsychological tests were performed. Participants showed increased levels of TNF- $\alpha$ , sTNF-R, IL-6, IL-1 receptor antagonist, and cortisol as well as decreased verbal and nonverbal memory functions after injection. Thus, these authors found a significant positive correlation between cytokine secretion and decreased memory performance in healthy adults.

Our study has several limitations. We did not study the circadian variability of cytokines and different findings might have emerged had we examined such variability in relation to neuropsychological performance.

While OSA severity variables were not significantly associated with cognitive functioning, this lack of association could possibly be due to limited statistical power. Nonetheless, our results suggest that inflammatory changes in OSA may have a more important impact on cognitive functioning than the breathing disorder per se.

We excluded patients with major medical illnesses other than OSA and hypertension. These criteria resulted in a population that may not be representative of OSA patients normally seen in a sleep clinic. While our population might thus not be considered as "typical" OSA patients, our exclusion criteria served to limit the impact of several potential confounders (e.g., diabetes) that could affect cognitive dysfunction.

Another limitation to our findings relates to the impact of obesity on inflammatory markers. It is possible that body fat may be an undetected confounder of the reported relationship between inflammation and cognitive function. While BMI was unrelated to cognitive functions (see Table 2), it must be acknowledged that we have a limited range of BMI in the sample (from 23.1 to 50.2 kg/m<sup>2</sup>, mean BMI 31.1 $\pm$ 0.9). It would actually be somewhat difficult to address this BMI-cognition-cytokine question in an apnea population for the following reasons: Apnea is strongly associated with increased BMI and thus nonobese apneics are relatively rare. On the other hand, if we enrolled apneics with severe obesity, we would be more likely to run into other confounding illnesses like diabetes, necessitating more complicated inferences regarding cognition. We have thus taken the middle course of studying moderate to severe apneics with moderate amounts of obesity. In an exploratory analysis, we included BMI as an independent variable in a hierarchical regression. The amount of explained variance in cognitive functioning did not increase beyond that observed in the previous model, and BMI was not a significant individual predictor. Therefore, to maximize power, we report the model that did not include BMI.

In conclusion, the findings of this study might help to disentangle the meaning of different types of factors that

**Table 3** Hierarchical linear regression analysis: global deficit score vs. markers of obstructive sleep apnea severity (AHI, %O<sub>2</sub><90) and sTNF-R1 ( $n=39$ )

	$\beta$	SE B	$t$ score	$p$ value
Step 1: forced entry of OSA severity variables <sup>a</sup> , $R^2=0.055$				
%O <sub>2</sub> <90	0.279	0.001	1.43	0.16
AHI	-0.130	0.002	-0.67	0.51
Step 2: forced entry of OSA severity variables plus sTNF-R1 <sup>b</sup> , $R^2=0.196$				
%O <sub>2</sub> <90	0.255	0.001	1.40	0.17
AHI	-0.120	0.002	-0.66	0.52
sTNF-R1	0.376	<0.001	2.48	0.02

<sup>a</sup> Model accounted for 5.5% of variance in global deficit score ( $F=1.04$ ,  $df=2$ , 37,  $p=0.36$ ).

<sup>b</sup> Model accounted for 19.6% of variance in global deficit score ( $F=2.84$ ,  $df=3$ , 36,  $p=0.05$ ).

affect cognition in OSA. While these findings must be considered preliminary, they nonetheless suggest that inflammation in OSA patients may be an important factor to consider in understanding cognitive functioning in these patients. However, because we had no prior data to suggest that sTNF-R1 would be the strongest predictor, replication of these findings is essential. Future studies might explore the effects of CPAP on cognition and inflammatory factors.

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