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SCIENTIFIC INVESTIGATIONS

Neuropsychological Effects of 2-Week Continuous Positive Airway Pressure Treatment and Supplemental Oxygen in Patients with Obstructive Sleep Apnea: A Randomized Placebo-Controlled Study

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Study Objectives: To determine predictors of neuropsychological functioning in patients with obstructive sleep apnea (OSA) and whether treatment with 2-week continuous positive airway pressure (CPAP) or supplemental oxygen would improve cognitive functioning.

Design: Randomized placebo-controlled design.

Setting: University-based clinical research center.

Patients: Forty-six patients with untreated OSA.

Interventions: Two-week CPAP, supplemental oxygen, or placebo-CPAP.

Measurements and Results: Participants underwent polysomnography and completed a neuropsychological test battery before and after treatment. Prior to treatment, patients with OSA showed diffuse impairments, particularly in terms of speed of information processing, attention and working memory, executive functioning, learning and memory, as well as alertness and sustained attention. A global deficit score at baseline was positively correlated with percentage of stage 1 sleep (p = .049) only and was not correlated with obesity, daytime sleepiness, depression, fatigue, OSA severity, and the other polysomnography variables. The 3 treatment groups (therapeutic-CPAP, supplemental oxygen, and placebo-CPAP) were compared using repeated-measures analysis of variance (ANOVA). There was no significant Time x Treatment interaction for the global deficit score. When examining individual neuropsychological test scores, two thirds of them improved with time regardless of treatment, although only Digit Vigilance—Time (p = .020) showed significant improvement specific to CPAP treatment.

Conclusion: The present results suggest that Digit Vigilance—Time might be the most sensitive neuropsychological test for measuring the effects of the treatments. In general, 2 weeks of CPAP or oxygen-supplementation treatment was insufficient to show overall beneficial cognitive effects, as compared with placebo-CPAP. However, 2 weeks of CPAP treatment might be helpful in terms of speed of information processing, vigilance, or sustained attention and alertness.

Keywords: Obstructive sleep apnea, neuropsychology, continuous positive airway pressure, oxygen supplementation, placebo, cognitive function

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Obstructive sleep apnea (OSA) can be a devastating illness, leaving patients exhausted from sleep deprivation. Some patients with OSA also have cognitive impairment[1]; however, the research results are mixed regarding the nature, cause, and extent of cognitive deficits in these patients.[2-8] Cognitive impairment in OSA seems to be exacerbated by the level of hypoxemia,[3,8-15] apnea hypopnea index (AHI),[9,10,12,16,17] and arousals,[9] but there is still some debate on which aspects of OSA are associated with cognitive impairment. Substantial proportions of patients with OSA also show clinical depression or mood alteration, irritability, lethargy, and tiredness.[18] Therefore, higher levels of depression[14] or fatigue[14], or less motivation might also influence the detection of decrements in neuropsychological test performance.

Continuous positive airway pressure (CPAP) treatment of OSA corrects the respiratory disturbances and the resultant transient desaturations.[13,15] Most research that has examined cognitive functioning before and after treatment with CPAP has reported improvements, but the findings are inconsistent.

In a previous study, we evaluated the effectiveness of 1-week CPAP treatment versus placebo-CPAP (ie, CPAP administered at subtherapeutic pressure) on cognitive functioning in patients with OSA. Although CPAP improved overall cognitive functioning, no beneficial effects in any specific domain were found. Indeed, only 1 of the 22 neuropsychological tests scores (Digit Vigilance—Time, a measure of speed of information processing, vigilance, or sustained attention and alertness) showed significant changes specific to CPAP treatment, a finding that could have occurred by chance. These findings might reflect an insufficient duration

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of the treatment trial (1 week) or, alternatively, they may imply powerful placebo effects of short-term CPAP therapy on cognitive functioning.[17]

The current study employs a design similar to that of our previous study but with 4 significant modifications. We lengthened the treatment time from 1 to 2 weeks. We modified the placebo-CPAP to provide less than 0.5 cm H_2O pressure at the nose. We assessed CPAP compliance using a hidden compliance clock and aggressively followed the patients to ensure compliance. Finally, we added nocturnal supplemental oxygen as a third treatment group.

In some patients with OSA who cannot tolerate CPAP and who are not candidates for a surgical procedure, supplemental oxygen therapy is often administered to reduce the harmful effects of transient desaturations during sleep.[19,20] Supplemental oxygen as a therapy for OSA and its effect on neuropsychological functioning have not been extensively evaluated, although supplemental oxygen has been reported to improve the subjective symptoms of OSA and reduce the Epworth Sleepiness Scale (ESS) score in uncontrolled studies[19]

This study thus investigated 2 questions: (1) What aspects of OSA best account for impairment of neuropsychological functioning? (2) In a double-blind trial, are the effects of CPAP different from those of supplemental oxygen or placebo-CPAP in terms of their impact on cognitive functioning?

METHODS

Participants

People with a history suggestive of sleep apnea were recruited by advertisement, word-of-mouth referral, referral from local medical practitioners in the San Diego area, and referral from previous participants. We limited enrollment to subjects in the age range of 30 to 65 years and with weight 100% to 200% of ideal body weight, as determined by Metropolitan Life Foundation height and weight tables.

Patients were excluded if they had a history of heart, liver, or renal disease, diabetes, psychosis, narcolepsy, current alcohol or drug abuse, severe asthma, or cerebrovascular disease. Pregnancy, as well as current prescription medications except antihypertensive medication, were additional exclusionary criteria. Patients receiving antihypertensive medication had their treatment tapered slowly in 2 to 3 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 mm Hg 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.

Experimental Design

All subjects were screened for sleep apnea using an unattended overnight home sleep-recording system study (Stardust; Respironics Inc., Marietta, GA). Subjects with an AHI of at least 15 were admitted to the General Clinical Research Center Gillin Laboratory of Sleep and Chronobiology for 3 nights. The subjects were told that they would receive 1 of the 3 treatments in a random fashion, and a brief description of each treatment was provided. None of the subjects had predominant central apneas (defined as when 50% or more of respiratory events are central). If the polysomnographic recording on the first night confirmed an AHI of at least 15, subjects were considered to have presumptive OSA and were invited to continue in the study.

On the second night of admission, subjects were randomly assigned to receive either traditional nasal CPAP (n = 17), placebo-CPAP (n = 14), or placebo-CPAP (n = 15) plus supplemental oxygen (for details on titration and treatment, see Apparatus section). Polysomnography was repeated on the third night of admission as subjects slept with their assigned treatment. The next morning, subjects were discharged home and instructed to use their assigned treatment (CPAP, placebo-CPAP, or supplemental oxygen) during sleep for 2 weeks.

In our previous study, 1 week of treatment resulted in improvement in overall neuropsychological functioning. However, improvement in any specific domain of functioning could not be confirmed. We speculated that longer treatment might result in further improvement. Treatment duration decisions in placebo-controlled trials must weigh the enhanced opportunity to observe effects with longer treatment against issues associated with keeping control subjects on placebo for a longer period. Thus, we received approval from the University of California, San Diego Institutional Review Board for 2 weeks of treatment.

After 2 weeks of treatment, the subjects were readmitted to the General Clinical Research Center to undergo a fourth overnight polysomnography with their assigned treatment. To verify the effectiveness of the blinding process, before discharge from the study, the subjects were asked what they thought their treatment assignment was. Approximately one third of the subjects on placebo or supplemental oxygen thought that they were receiving CPAP or subjectively felt better. Approximately one third had no opinion as to their therapy assignment, and one third correctly guessed their treatment assignment at completion of the study. The technicians who scored the sleep studies, the research staff administering the neuropsychological testing, and the investigators were blinded to the randomization assignments.

Apparatus

Sleep Recordings

Sleep was monitored on the General Clinical Research Center with the Grass Heritage digital polysomnograph (Model PSG36-2, Astro-Med, Inc, West Warwick, RI). Central and occipital electroencephalogram, bilateral electrooculogram, submental and tibialis anterior electromyogram, electrocardiogram, body position, nasal airflow using a nasal cannula/pressure transducer, and oral airflow using a thermistor were assessed. Respiratory effort was measured using chest and abdominal piezoelectric belts. Oxyhemoglobin saturation (Sa_{O_2}) was monitored using a pulse oximeter (Biox 3740; Ohmeda: Louisville, Colo) and scored with Profox Software (Profox; Escondido, Calif). Sleep records were manually scored according to the criteria of Rechtshaffen and Kales.[21] AHI was calculated as the average of the total number of apneas (decrements in airflow of ≥ 90% from baseline for ≥ 10 seconds) and hypopneas (decrements in airflow of ≥ 50% but < 90% from baseline for ≥ 10 seconds) experienced per hour of sleep.[13]

CPAP, Placebo-CPAP, and Supplemental Oxygen

Equipment for all 3 treatment arms was similar, consisting of a CPAP machine (Aria LX CPAP System, Respironics Inc., Murrysville, Penn), CPAP mask (Respironics Profile Light), a heated humidifier (Fisher and Pykel HC100, Auckland, New Zealand), and an oxygen concentrator (Alliance, Healthdyne Technologies Model 505, Marietta, GA) that could be switched to produce either room air or oxygen.

In the CPAP group, subjects received active CPAP plus an oxygen concentrator that provided room air. On the second night in the General Clinical Research Center, optimal effective nasal CPAP pressure to minimize sleep apnea was obtained by conventional manual overnight CPAP titration during monitoring with polysomnography. All subjects randomly assigned to CPAP had effective titration.

Subjects assigned to placebo-CPAP and supplemental oxygen underwent a mock titration on the second night using a modified version of the sham-CPAP system reported by Farre et al.[22] Those assigned to placebo-CPAP received subtherapeutic CPAP (CPAP < 0.5 cm H_2O at the mask) plus an oxygen concentrator that provided room air. A modified CPAP mask, containing 10 one-quarter–inch drill holes to allow for adequate gas exchange with room air, was used while the CPAP pressure was set at a constant 3 cm H_2O. With this system, the pressure at the CPAP mask was 0.5 cm H_2O at end expiration and 0 cm H_2O during inspiration, and the patient was able to feel a gentle breeze at the nose. Those assigned to nocturnal supplemental oxygen received subtherapeutic CPAP plus an oxygen concentrator delivering oxygen at 3 L per minute.

All CPAP units had a hidden compliance clock, which allowed measurement of the nightly time the CPAP units were switched on. Compliance for all 3 treatment arms was assessed as mean hours per night across the 2-week treatment period. All 3 arms of the study showed similar compliance levels (p = .373): Placebo-CPAP = 6.0 ± 1.4 h/night (range = 3.5 - 8.3); CPAP = 6.6 ± 1.2 h/night (range = 3.7 - 8.6); oxygen supplementation = 6.6 ± 1.4 h/night (range = 3.9 - 8.4). For the oxygen-supplementation group, oxygen was automatically supplied when the CPAP machine was turned on; thus, oxygen compliance was equal to CPAP compliance in that group.

Measures

Neuropsychological Tests

Subjects were given the following battery at baseline and after 2 weeks of treatment: Wechsler Adult Intelligence Scale-Rev,[23] Digit Symbol, Digit Span, Letter-Number Sequencing, Symbol Search; Brief Visuospatial Memory Test-Rev[24]; Hopkins Verbal Learning Test-Rev[25]; Trail Making A/B[26]; Digit Vigilance[27]; Stroop Color-Word[28]; and Word Fluency.[29] These tests produced 15 subscale scores per subject and assessed the following cognitive domains: speed of information processing (Digit Symbol, Symbol Search, Digit Vigilance, Trail Making A, Stroop color); attention and working memory (Letter-Number Sequencing, Digit Span, Digit Vigilance); executive functions (Trail Making B, Digit Symbol, Symbol Search, Letter-Number Sequencing, Stroop Color-Word); alertness and sustained attention (Digit Vigilance); verbal learning and memory (Hopkins Verbal Learning Test-Rev), verbal short-term memory and working memory (Digit Span, Letter-Number Sequencing); visuospatial memory (Brief Visuospatial Memory Test-Rev); and, psychomotor performance (reaction times on the tests). The tests were administered at 1 PM by the same research personnel and required approximately 60 minutes to complete.

Daytime Sleepiness

Subjects completed the Epworth Sleepiness Scale (ESS) to rate their subjective daytime sleepiness. The ESS is an 8-item questionnaire that asks patients to answer each question from 0 (not at all likely to fall asleep) to 3 (very likely to fall asleep), yielding a score of 0 (minimum) to 24 (maximum).[30]

Psychological Evaluation

Participants completed the Profile of Mood States[31] at intake into the study. The reliabilities of the Profile of Mood States subscales are well established; we were interested in the Depression, Fatigue, Tension, Anger, Confusion, and Vigor subscales of the Profile of Mood States.

Data Analyses

Raw scores were calculated for each neuropsychological subtest. To investigate how many patients with OSA had neuropsychological impairment, and in what domains, T-scores were calculated for the neuropsychological subtests for which normative data were available (controlling for ethnicity, sex, age, and education). Higher T-scores indicate better performance. A deficit score was computed for each of the 15 individual test scores, according to the convention below, in which T-scores are collapsed into groups from 0 to 5. The average of those scores is the global deficit score (GDS): with a GDS of 40 or higher, the T-score is 0; 35 or higher but less than 40, is 1; 30 or higher but less than 35, is 2; 25 or higher but less than 30, is 3; 20 or higher but less than 25, is 4; 19 or less, is 5.

Pearson correlations were used to determine the association between the baseline GDS and body mass index, scores on the ESS, scores for Profile of Mood States subscales, and sleep variables.

Differences among and within the 3 treatment groups over time were assessed using repeated-measures ANOVA using raw data and then using T-scores. This analysis allowed testing for main effects of treatment (CPAP vs placebo-CPAP vs supplemental oxygen), time (prior to treatment vs after 14 days of treatment) and the interaction of time by treatment. A time effect alone would imply that the treatment itself had no specific effect on the variable of interest. On the other hand, a treatment-by-time interaction would imply that 1 of the treatment groups responded to treatment over time differently than did the other treatment groups.

Statistical analyses were performed using SPSS statistical software (SPSS for Windows 12.0: SPSS Inc.; Chicago, Ill). Statistics were considered significant at $p < .05$.

RESULTS

Clinical characteristics of the subjects are presented in Table 1. The subjects were, on average, obese, with an average body mass index of 30.9 ± 5.9 kg/m^2. Also, subjects had significant daytime

Table 1—Baseline Demographic and Sleep Data in Total Subjects[a]

	Placebo (n = 14)	CPAP (n = 17)	Oxygen (n = 15)	p Value
Age, y	48.9 ± 3.2	46.7 ± 2.4	47.1 ± 2.3	0.817
Body Mass Index, kg/m^2	30.8 ± 1.9	31.7 ± 1.4	30.2 ± 1.2	0.787
Screening blood pressure, mm Hg				
Systolic	129.3 ± 17.3	135.5 ± 15.3	134.8 ± 13.8	0.319
Diastolic	79.2 ± 12.5	80.5 ± 8.9	80.4 ± 9.9	0.889
Apnea Hypopnea Index	65.8 ± 8.2	63.5 ± 7.8	58.6 ± 8.3	0.818
Average oxygen saturation	92.3 ± 1.3	93.1 ± 1.1	93.2 ± 1.4	0.845
Epworth Sleepiness Scale, score	12.9 ± 2.0	11.2 ± 1.0	9.4 ± 1.7	0.313

[a]Data are reported as mean ± SEM

somnolence at baseline as reflected by the ESS score of 11.2 ± 5.7. There were no significant differences among the 3 groups in age, body mass index, screening blood pressure, AHI, average oxygen saturation, or ESS scores at baseline (Table 1).

To fully assess the efficacy of supplemental oxygen therapy, we compared average oxygen scores by treatment group over time using repeated-measures ANOVA. A significant Time x Treatment interaction emerged (p = .010). In posthoc analyses (using the Least Significant Difference method to correct for multiple comparisons), the groups did not differ in average oxygen saturation at baseline. However, average oxygen scores were significantly higher after treatment for the CPAP (96.2% ± 2.8%, p < .001) and oxygen-supplementation (95.9% ± 3.5%; p = .001) groups when compared with the placebo group (91.2% ± 4.1%). In addition, although the placebo group showed no significant change in average oxygen saturation from before to after treatment (p = .257), the CPAP (p = .003) and oxygen-supplementation (p = .025) groups showed significant improvement.

Using normative scores, we investigated how many patients with OSA showed neuropsychological impairment; T-scores less than 40 were designated as "impaired." These patients with OSA showed diffuse impairments, particularly in terms of executive functioning, verbal learning and memory, and alertness and sustained attention (Table 2).

Table 2—Percentage of Subjects With Impaired Neuropsychological Functioning Before Treatment

Neuropsychological Test	%[a]
Digit Symbol, no. correct	17.8
Symbol Search, no. correct	6.5
Digit Vigilance, time	2.2
Trail Making A, time	15.2
Stroop Color, no. correct	42.2
Letter/Number Sequencing, no. correct	6.5
Digit Span Total	8.7
Digit Vigilance, no. of errors	26.1
Trail B, time	15.2
Stroop Color-Word, ratio	6.7
Brief Visuospatial Memory Test-Rev--TR	8.7
Hopkins Verbal Learning Test-Rev--TR	26.1
Brief Visuospatial Memory Test-Rev--DR	2.2
Hopkins Verbal Learning Test-Rev--DR	28.3
Word Fluency, Total	30.4

[a]Percentage of subjects with < 40 T-score, implying impaired neuropsychological functioning in the tests before Treatment (ie, therapeutic-continuous positive airway pressure [CPAP], oxygen supplementation, or placebo-CPAP). TR refers to total recall; DR refers to delayed recall.

Table 3 summarizes the Pearson correlation coefficients between GDS and the variables of interest. The baseline GDS was significantly associated with percentage of stage 1 sleep (r = .292, p = .049) only.

Tables 4 and 5 show pretreatment and posttreatment means for the neuropsychological test raw and T-scores (respectively) in the 3 groups. Using repeated-measures ANOVA with raw data, significant changes over time, regardless of treatment, were observed for Digit Symbol—Number Correct, Symbol Search—Number Correct, Digit Vigilance—Time, Trail Making A—Time, Stroop Color—Number Correct and Ratio, Letter-Number Sequencing, Trail Making B—Time, Brief Visuospatial Memory-Rev—Delayed Recall, and Word Fluency—Total scores. However, when examining Time × Treatment interactions, only Digit Vigilance—Time (p = .020) showed significant improvement specific to CPAP treatment (Table 4).

When we repeated the analysis with T-scores, similar findings were observed. Significant changes over time, regardless of treatment, were observed for Digit Symbol—Number Correct, Digit Vigilance—Time, Trail Making A—Time, Stroop Color—Number Correct, Letter-Number Sequencing, Digit Span—Total,

Table 3—Univariate Correlations

Correlation of GDS[a] with:	**r**	**p Value**
Body Mass Index	0.072	0.633
Epworth Sleepiness Scale	0.102	0.532
Profile of Mood States, subscale		
Depression	0.138	0.378
Fatigue	0.153	0.329
Tension	0.090	0.562
Anger	-0.033	0.833
Confusion	0.047	0.766
Vigor	-0.057	0.717
Apnea Hypopnea Index	0.046	0.763
Average oxygen saturation	-0.192	0.200
% of time at Sao_2 < 90%	0.236	0.114
Total Arousal Index	0.100	0.515
Sleep stage, %		
1	0.292	0.049
2	-0.283	0.056
SWS	0.091	0.546
REM	-0.183	0.223
WASO, min	0.094	0.540

[a]Global deficit score (GDS): each individual test score is computed into a deficit score and the average of those scores is the GDS. Higher GDS scores indicate poorer performances. SWS refers to slow-wave sleep; REM, rapid eye movement sleep; WASO, wake after sleep onset.

Table 4—Mean Neuropsychological Test Scores Using Raw Data

Neuropsychological Test	Placebo (n = 14)		CPAP (n = 17)		Oxygen (n = 15)		P Value[a]	
	Pre	Post	Pre	Post	Pre	Post	Time	Treatment[b]
Digit Symbol, no. correct	67.6	68.7	65.8	73.8	73.9	77.9	0.014	0.256
Symbol Search, no. correct	32.1	37.7	31.8	33.8	33.3	35.9	0.036	0.614
Digit Vigilance, time[b]	326.4	303.1	350.9	312.3	314.1	313.4	< 0.001	0.020
Trail Making A, time[b]	25.5	21.7	32.4	26.5	29.1	24.7	< 0.001	0.494
Stroop Color, no. correct	73.7	77.9	67.7	72.3	66.7	76.7	0.007	0.532
Letter/Number Sequencing	11.7	12.9	11.0	11.9	11.1	11.7	0.005	0.827
Digit Span Total	21.2	22.5	18.6	26.4	19.3	21.3	0.091	0.378
Digit Vigilance, no. errors[b]	14.1	10.6	5.6	7.2	8.9	7.3	0.196	0.080
Trail Making B, time[b]	70.3	59.6	70.8	63.4	66.8	60.7	0.010	0.823
Stroop Color-Word ratio	37.9	41.9	37.7	37.3	40.1	44.2	0.007	0.061
Brief Visuospatial Memory Test-Rev--TR	26.1	25.7	26.4	29.7	27.0	28.2	0.073	0.143
Hopkins Verbal Learning Test-Rev--TR	26.3	25.5	24.7	24.2	27.9	28.6	0.679	0.486
Brief Visuospatial Memory Test-Rev--DR	10.5	9.4	10.8	10.7	10.7	10.5	0.022	0.138
Hopkins Verbal Learning Test-Rev--DR	9.0	8.3	8.9	8.8	9.8	9.8	0.347	0.641
Word Fluency Total	42.3	45.5	38.4	40.9	37.0	44.3	< 0.001	0.149

[a]p Values are listed for effects on the time x treatment interaction.
[b]Lower scores indicate better performances. TR refers to total recall; DR refers to delayed recall.

Trail Making B—Time, Brief Visuospatial Memory-Rev—Delayed Recall, and Word Fluency—Total. However, when examining Time × Treatment interactions, again, only Digit Vigilance—Time (p = .020) showed significant improvement specific to CPAP treatment. There was no significant Time × Treatment interaction for the GDS.

DISCUSSION

This paper had 2 different foci. The first aim was to determine which OSA-related variables were associated with neuropsychological deficits in OSA. We thought that this knowledge might help in the design of future studies that evaluated the potential reversibility of such deficits after OSA treatment.

Prior to treatment, these patients with OSA showed diffuse impairments, particularly in terms of executive functioning, verbal learning and memory, and alertness and sustained attention. Although the GDS—a measure of overall cognitive functioning—was correlated with stage 1 sleep, it was not associated with obesity, daytime somnolence, mood, arousals, or severity of OSA. However, this significant association could have occurred by chance, given the number of OSA-related variables examined. In fact, posthoc correction for multiple comparisons resulted in these associations being nonsignificant.

OSA is characterized by repeated episodes of upper-airway obstruction during sleep, which is associated with intermittent hypoxemia, transient arousals, disruption of sleep, and excessive daytime sleepiness.[1-5] The pathogenesis of cognitive deficits is controversial and most likely multifactorial. Although several authors have reported that severity of hypoxemia and chronic intermittent oxyhemoglobin desaturation are associated with reduction in general intellectual measures, verbal fluency, psychomotor

Table 5—Mean Neuropsychological Test Scores Using T-Scores

Neuropsychological Test	Placebo (n = 14)		CPAP (n = 17)		oxygen (n = 15)		p Value[a]	
	Pre	Post	Pre	Post	Pre	Post	Time	× Treatment
Digit Symbol, no. correct	49.1	51.8	45.7	50.3	53.6	56.9	< 0.001	0.202
Symbol Search, no. correct	51.3	52.9	49.8	52.7	54.4	57.5	0.066	0.887
Digit Vigilance, time[b]	59.7	63.4	54.7	64.2	61.2	61.4	< 0.001	0.020
Trail Making A, time[b]	52.5	58.1	44.6	50.5	48.2	55.1	< 0.001	0.888
Stroop Color, no. correct	47.1	51.0	46.4	48.2	46.0	52.8	0.001	0.225
Letter/Number Sequencing	47.4	57.7	42.0	54.3	42.2	53.6	< 0.001	0.888
Digit Span Total	59.6	63.3	51.8	56.6	53.9	59.2	< 0.001	0.837
Digit Vigilance, no. errors[b]	40.1	43.9	48.4	47.7	45.8	48.3	0.193	0.387
Trail Making B, time[b]	51.0	56.1	50.6	53.6	49.6	54.3	0.009	0.829
Stroop Color-Word ratio	46.4	50.9	48.9	46.1	49.1	51.1	0.487	0.215
Brief Visuospatial Memory Test-Rev--TR	52.9	54.7	53.3	59.3	53.6	56.1	0.163	0.109
Hopkins Verbal Learning Test-Rev--TR	46.3	44.7	42.4	40.8	49.3	50.8	0.654	0.542
Brief Visuospatial Memory Test-Rev- -DR	57.6	51.9	58.4	57.6	57.7	56.3	0.020	0.150
Hopkins Verbal Learning Test-Rev--DR	46.1	43.2	44.5	43.3	48.7	48.5	0.348	0.776
Word Fluency Total	49.3	52.8	45.7	48.5	45.4	51.9	< 0.001	0.268
Global Deficit Scores[c]	0.289	0.267	0.361	0.274	0.213	0.177	0.205	0.754

[a]p Values are listed for the effects of time and the time × treatment interaction.
[b]Higher T-scores indicate better performances.
[c]Higher Global Deficit Scores indicate poorer performances. TR refers to total recall; DR refers to delayed recall.

performance, and executive tasks in OSA,[5,8,10] having lower oxyhemoglobin saturation during sleep has not always been found to be correlated with daytime cognition.[32,33] Moreover, the results of our study are in agreement with the previous research of Redline et al, who reported no significant relationship between neuropsychological performance and sleepiness.[34]

The second aim of our study was to determine whether 2-week CPAP or supplemental-oxygen treatment would improve neuropsychological test performance compared with placebo-CPAP treatment. Using repeated-measures ANOVA, we did not find a significant Time × Treatment interaction for the GDS. When examining individual neuropsychological tests, significant changes over time regardless of treatment were observed for 9 of the 15 subtests. However, only Digit Vigilance—Time ($p = .020$) showed a significant improvement specific to CPAP treatment. It is possible that this finding occurred by chance. However, it is the same test observed to be responsive to CPAP treatment in our prior study [17] and the same domain of functioning responsive to CPAP treatment in a study by Ferini-Strambi et al. [35] This suggests that this aspect of neuropsychological functioning may be particularly sensitive to CPAP treatment. No tests showed effects specific to oxygen supplementation or placebo-CPAP treatments.

These results are consistent with those of our previous study,[17] which also found significant specific effects of 1 week of CPAP treatment on Digit Vigilance—Time. The Digit Vigilance test is a paper-and-pencil task designed to measure speed of information processing, sustained attention, and alertness during rapid visual tracking and accurate selection of target stimuli.[27] Our consistent findings across 2 separate studies suggest that Digit Vigilance—Time might be the most sensitive neuropsychological test for measuring response to treatment. Our results are also in agreement with those of the study by Ferini-Strambi et al,[35] although they had a different design with no placebo control. The placebo control in our study is important. Had we not controlled for placebo effects, we would erroneously have concluded that CPAP led to significant improvement in almost half of our neuropsychological tests.

Because cognitive impairment in patients with OSA may lead to poor work[36] or school[37] performance and an increased risk of motor vehicle accidents,[38] there has been an interest in the neuropsychological evaluation of patients with OSA. In patients with OSA, diverse neuropsychological tests have been used to examine cognitive dysfunction, with deficits in vigilance, attention, concentration, memory, learning ability, executive functions, visuoconstruction ability, and motor performance being reported.[10,11,17,39,40]

To lessen the participant burden, we chose a neuropsychological test battery that required 60 minutes to complete. We measured several important areas of cognition[18,25,35,41]: speed of information processing, attention and working memory, executive functions (eg, cognitive set shifting, inhibition, and selective attention), alertness and sustained attention, verbal learning and memory, visuospatial memory, and psychomotor performance. Our current findings, coupled with similar findings in our prior report, suggest that speed of information processing, vigilance, or sustained attention and alertness—aspects of neuropsychological functioning critical to work performance and motor vehicle operation—are specific cognitive domains that may respond to CPAP treatment in patients with OSA.

A substantial number of the subjects, regardless of treatment type, improved over time in both our previous and present studies. This may reflect a learning effect in response to repeated neuropsychological testing, particularly given the relatively brief time between assessments (2 weeks).

Results of our present study differed somewhat from those in our previous study. In the previous study, we found a subtle but significant improvement in overall cognitive performance in individuals who received CPAP, compared with those who received placebo-CPAP. However, in the present study, we observed no significant Time × Treatment interaction for the GDS. The improvement in overall neuropsychological ranking that we observed in our previous study could have happened by chance. It may have been due to the fact that the CPAP effect occurred within the first week of treatment or that placebo effects could be weaker in the second week of therapy. The current study cannot disentangle these questions. These more-recent findings suggest that there is no significant difference of the effect in global deficits between 2 weeks of CPAP treatment, nocturnal oxygen supplementation, and placebo-CPAP. However, 2 weeks of CPAP treatment might be helpful in the domains of speed of information processing, alertness, and sustained attention (as measured by Digit Vigilance—Time). However, it is possible that treatment longer than 2 weeks might be required to observe changes in neuropsychological functioning specific to CPAP or oxygen-supplementation treatment.

These findings argue for the importance of a number of considerations in future studies, foremost of these is the placebo effect. Unless studies include a placebo control, they are vulnerable to a mistaken attribution of "benefit" to a specific treatment. The key statistical question addressed by this study was the time-by-treatment interaction. Such interaction terms are notoriously unstable, and thus replication (and with a larger sample size) is desired. Finally, neuropsychological tests can be influenced by learning effects. Even though we employed alternate forms for such tests, learning effects may complicate the interpretation of findings. Clearly, neuropsychological tests for such a design are best when they are less affected by such test-retest considerations.

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