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A Model for Studying Neuropsychological Effects of Sleep Intervention: The Effect of 3-week Continuous Positive Airway Pressure Treatment

In-Soo Lee, M.D.¹, Wayne A. Bardwell, Ph.D.¹, Rujvi Kamat, B.S.², Lianne Tomfohr, B.A.², Robert K. Heaton, Ph.D.¹, Sonia Ancoli-Israel, Ph.D.¹, Jose S. Loreda, M.D.³, and Joel E. Dimsdale, M.D.¹

¹Department of Psychiatry, University of California San Diego

²San Diego State University/University of California, San Diego Joint Doctoral Program in Clinical Psychology

³Department of Medicine, University of California San Diego

Abstract

Purpose—Patients with obstructive sleep apnea (OSA) commonly have cognitive complaints. There are few randomized studies that have examined neuropsychological effects of continuous positive airway pressure (CPAP) treatment in patients with OSA. In this double-blind trial, we examined if a 3-week CPAP treatment compared with placebo CPAP treatment has specific therapeutic effects on cognitive impairments in patients with OSA and if there are specific domains of cognitive impairments sensitive to 3-week CPAP treatment.

Subjects and methods—Thirty-eight newly diagnosed patients with untreated OSA underwent neuropsychological testing before and after 3-weeks CPAP or Placebo CPAP treatment. The two treatment groups (therapeutic CPAP, and placebo-CPAP) were compared using repeated measures analysis of variance (ANOVA).

Results and conclusion—Impairments in neuropsychological functioning ranged from 2.6% to 47.1% before treatment. In response to 3 weeks of treatment, there was no significant time by treatment interaction for a global deficit score of neuropsychological functioning. Only the Stroop Color (number correct) test showed significant improvement specific to CPAP treatment. The study demonstrates the importance of further randomized placebo controlled studies in this area.

Keywords

obstructive sleep apnea; CPAP; cognitive function; double blind placebo-controlled; neuropsychological test; Stroop color

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Corresponding author: In-Soo Lee, M.D., Tel: +1-619-543-5592, Fax: +1-619-543-5462, insoolee2006@gmail.com, islee@ucsd.edu, Mailing Address: UC San Diego, 9500 Gilman drive, La Jolla, California 92093-0804.

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Introduction

Studying cognitive function in sleep disorders and their treatment requires meticulous attention to experimental design. This paper considers such design issues in the context of a randomized clinical trial. Obstructive sleep apnea (OSA) is a chronic condition characterized by repetitive upper airway obstruction, recurrent arousals, apneic episodes, and hypoxemia during sleep¹. It is a common disorder^{2, 3} that is associated with considerable morbidity and mortality, particularly from hypertension, cardiovascular disease, and insulin resistance^{4, 5}. Furthermore, the excessive daytime sleepiness associated with OSA can result in increased risk for automobile⁶ or industrial accidents⁷.

Cognition is frequently impaired in OSA. Considerable research has examined the associated neuropsychological deficits. Impairments in vigilance, executive function, and motor coordination have been consistently reported, but the effects of OSA on visual and motor skill and memory functioning have been less clear^{8, 9}. The pathogenesis of cognitive deficits in OSA is controversial and most likely multifactorial. The two most commonly suggested mechanisms are repetitive sleep fragmentation and nocturnal hypoxemia. However, underlying mechanisms such as inflammation may also be very relevant⁹.

One of the major issues about cognitive impairment in OSA is whether treatment corrects the deficits. Many studies have examined cognitive functioning after treatment for OSA has been initiated¹⁰. Treatment effects have been inconsistent for sustained attention, attention/vigilance, memory, executive functioning, psychomotor function, as well as constructional abilities or psychomotor functioning⁹. In some uncontrolled studies, CPAP treatment had a moderate to large effect on cognitive processing, memory, sustained attention, and executive functions¹¹.

However, other studies show persistent cognitive deficits despite treatment^{12, 13}. Unfortunately, there are few randomized placebo-controlled trials designed to address this issue, and only four of them compared CPAP with placebo-CPAP. The findings have been contradictory and in no way conclusive. Some controlled clinical trials evaluating the efficacy of CPAP treatment suggested that beneficial CPAP treatment effects for cognition might be attributable to changes in the underlying level of daytime sleepiness^{14, 15}. Previously, our group evaluated the effectiveness of 1-week CPAP treatment versus placebo-CPAP (i.e., CPAP administered at sub-therapeutic pressure) on cognitive functioning in patients with OSA. Although CPAP improved overall cognitive functioning, no beneficial effects in any specific domain were found. Moreover, only 1 of the 22 neuropsychological tests scores (Digit Vigilance—Time) showed significant changes specific to CPAP treatment¹⁶. We replicated this study in a second sample of apneic patients who were studied in response to 2-weeks of CPAP treatment. Two thirds of neuropsychological test scores improved with time regardless of treatment; however, once again, only Digit Vigilance—Time showed significant improvements that were specific to CPAP treatment¹⁷. We wondered if 2-week CPAP treatment was insufficient to show overall beneficial cognitive effects, as compared with placebo-CPAP; thus, this study examined OSA patients who were randomized double blind to 3-weeks of either CPAP or placebo-CPAP therapy using the same neuropsychological tests batteries consistent with our previous studies.

In this double-blind trial, we examined 1) The extent of cognitive impairments in an apneic sample prior to treatment. 2) If the 3-week CPAP treatment has specific therapeutic effects on cognitive impairments in patients with OSA compared with placebo effects of CPAP treatment. 3) If there are specific domains of cognitive impairments sensitive to 3-week CPAP treatment.

Methods

Participants

Thirty-eight CPAP naïve men and women with obstructive sleep apnea were studied as part of a randomized double blinded clinical trial comparing three weeks of treatment with therapeutic CPAP compared to an optimized Placebo CPAP. Subjects were recruited by advertisement and word-of-mouth referral. Subjects were excluded if they reported a history of major medical illnesses (other than OSA and hypertension), had a current psychiatric diagnosis, were receiving psychotropic or sedative hypnotic medication, were currently pregnant, or if they had ever received treatment for OSA. Subjects who were receiving anti-hypertensive medications (n=2) had their medications slowly tapered and participated after a 3-week Washout period. The protocol was approved by the University of California San Diego (UCSD) Human Subjects Institutional Review Board, and all subjects provided written informed consent.

Procedure

Initial OSA screening was conducted with an unattended home sleep study (Stardust II home monitoring system, Resironics Inc). Subjects with an apnea hypopnea index (AHI) ≥ 10 were given a provisional diagnosis of OSA and were admitted to the UCSD General Clinical Research Center Gillin Laboratory of Sleep and Chronobiology at 17:00 hours for assessment. On their first night in the hospital, subjects had their sleep monitored by polysomnography from 22:00 to 6:00 hours the next morning. Those subjects who still had an AHI ≥ 10 were diagnosed with OSA and randomized to receive either therapeutic CPAP or placebo CPAP in a double-blinded fashion. Only the night sleep technicians and technicians providing home visits were not blinded to the intervention and did not participate in the outcome assessment.

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. Pulse oximetry at the finger was used to measure transient drops in oxyhemoglobin saturation. Sleep records were manually scored according to the criteria of Rechtschaffen and Kales¹⁸. Apneas were defined as decrements in airflow of $\geq 90\%$ from baseline for ≥ 10 s. Hypopneas were defined as decrements in airflow of $\geq 50\%$ but $< 90\%$ from baseline for ≥ 10 s regardless of the presence or absence of significant desaturations ($\geq 3\%$) or microarousals. The numbers of apneas and hypopneas per hour were calculated to obtain the apnea hypopnea index (AHI). Subjects with an AHI ≥ 10 were considered to have OSA and were admitted to the study. Transient oxyhemoglobin desaturations of $\geq 3\%$ from their immediate baseline lasting at least 10 seconds were scored and analyzed to obtained the oxyhemoglobin desaturation index (ODI), the number of desaturations per hour of sleep.

On the following night, subjects were randomized to receive either CPAP titration or mock-CPAP titration. All subjects then spent a second night in the sleep lab. Subjects randomized to receive therapeutic CPAP underwent standard CPAP titration. CPAP was started at a pressure of 4cm H₂O and was increased by 1-2cm H₂O increments based on the presence of apneas, hypopneas, snoring or respiratory effort related arousals. Titration was considered successful when all significant respiratory events stopped and the patient had spent at least 15 minutes of sleep in the final CPAP level.

Subjects randomized to the placebo CPAP group underwent a mock titration night. The placebo CPAP system was a modified version of the sham-CPAP reported by Farre et al¹⁹. This placebo CPAP consisted of a modified nasal or full face (nasal oral) CPAP mask with ten ¼ inch drill holes to allow free exchange of air during inhalation and exhalation, plus a pressure reducer placed in the CPAP tubing. With this system the CPAP generator could be placed at any pressure to control for machine noise, but the pressure at the nose and mouth was 0.5 cm water during exhalation and 0 cm water during inhalation. Of importance to the placebo CPAP blinding, the subject was able to feel a gentle breeze at the nose. In both treatment conditions, the CPAP systems were the same (ResMed S7 Elite CPAP with HumidAire 2i™ integrated heated humidifier; ResMed Corp. San Diego, CA). On the first night, the appropriate CPAP mask (therapeutic or placebo) was fitted and the patient was trained on the use of the equipment.

Subjects then continued their treatment (CPAP or Placebo CPAP) at home for three weeks. Proper equipment use and setup was monitored by scheduled telephone calls and home visits by a sleep technician who was not involved in the outcome assessments. Subjects received frequent reminders to comply with treatment, and hours used per day was logged on the CPAP machine and analyzed at the end of the treatment period. After three weeks of treatment, subjects returned for a repeated assessment of neurocognitive functioning.

Measures

Neuropsychological Tests—At 1 P.M. on the day after the first night of polysomnography, subjects were given the following battery at baseline: Wechsler Adult Intelligence Scale III,²⁰ Digit Symbol, Digit Span, Letter-Number Sequencing, Symbol Search; Brief Visuospatial Memory Test-Rev,²¹ Hopkins Verbal Learning Test-Rev,²² Trail Making A/B,²³ Digit Vigilance,²⁴ Stroop Color-Word,²⁵ and Word Fluency²⁶. The battery was repeated after 3 weeks of treatment. These tests produced 15 variables per subject and assessed the following cognitive domains: speed of information processing (Digit Symbol, Symbol Search, Digit Vigilance-Time, Trail Making A, Stroop color); attention and working memory (Letter-Number Sequencing, Digit Span, Digit Vigilance-Errors); executive functioning (Trail Making B, Digit Symbol, Symbol Search, Stroop Color-Word Interference Trial); verbal learning and memory (Hopkins Verbal Learning Test-Rev), visuospatial learning and memory (Brief Visuospatial Memory Test-Rev); and, psychomotor performance (reaction times on the tests). The tests were administered 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)²⁷.

Psychological Evaluation—Because neuropsychological functioning can be affected by depression and fatigue levels, we also assessed these constructs using the Center for Epidemiologic Studies-Depression (CES-D) Scale and the Multidimensional Fatigue Symptom Inventory-short form (MFSI-sf) total score.

The Center for Epidemiologic Studies-Depression (CES-D) Scale is a 20-item self-report scale that has been shown to be reliable and valid for assessing depressive symptoms²⁸. CES-D scores of 16 or above are considered indicative of depressed mood. The CES-D primarily taps cognitive/affective aspects of depression and has been shown to be useful in chronically ill groups, including OSA patients. Patients were instructed to fill out the CES-D according to how they felt in the past year.

The Multidimensional Fatigue Symptom Inventory-short form (MFSI-sf) is a 30-item self-report measure designed to assess the principal manifestations of fatigue, yielding a total fatigue score with a full range from -24 to 96. Thus, in the case of low fatigue and high vigor, the total score can be negative. Studies in patients with cancer found that a mean MFSI-sf total score >0.85 were associated with significant fatigue²⁹.

Data Analyses—All participants completed a neurocognitive evaluation with a comprehensive neuropsychological battery designed to assess functioning in 7 ability domains. Raw test scores were converted to T scores (standard scores with a mean of 50 and standard deviation of 10) using demographically corrected norms to account for the effects of age, education, gender, and ethnicity, as available for each measure. Individual test T-scores < 40 (more than one standard deviation below the mean) are considered impaired. The mean T-scores for each of the 7 domains were converted into deficit scores (0-5), and all scores in the battery were averaged to give the Global Deficit Score (GDS). With a T-score ≥ 40, the GDS is 0 (normal). Other T-score cutpoints and their corresponding GDS are as follows: 40 > T-score ≥ 35, is 1 (mildly impaired); 35 > T-score ≥ 30, is 2 (mildly to moderately impaired); 30 > T-score ≥ 25, is 3 (moderately impaired); 25 > T-score ≥ 20, is 4 (moderately to severely impaired); 19 ≥ T-score, is 5 (severely impaired). As described previously, GDS ≥ 0.5 are defined as “globally impaired”, and GDS < 0.5 as non-impaired³⁰. In other words, to meet criteria for “impaired”, a subject had to demonstrate, on average, at least mild deficits (e.g., deficit score of ≥ 1, representing a T score < 40) on at least half of the 15 neuropsychological subtests (or in at least two ability areas)³¹. This method of ascertaining neurocognitive impairment has been used extensively by several national multi-site studies of HIV-associated deficits, as well as with schizophrenic patients³² and chronic obstructive pulmonary disease³³. It has the advantage of providing data reduction to minimize multiple comparisons, and it has shown robust relationships with documented brain injury³⁴.

Student t-tests were employed to compare the means of demographic variables, sleepiness, depression, fatigue level, and apnea severity between both groups before treatment.

Pearson correlations were used to determine the association between the baseline GDS and body mass index (BMI), scores on the ESS, scores for CES-D, MFSI-total, and sleep variables.

Differences among and within the 2 treatment groups over time were assessed using repeated-measures ANOVA using sleep variables, T-scores on the entire battery, and on the individual tests. This analysis allowed testing for main effects of treatment (CPAP vs. placebo-CPAP), time (prior to treatment vs. after 3 weeks 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 (i.e. a placebo effect or “practice effect” on cognitive tests). On the other hand, a treatment-by-time interaction would imply that 1 of the treatment groups responded to treatment over time differently than the other treatment group.

Data were analyzed using SPSS 17.0 software (Chicago, IL, 2009). Statistical significance was set at $p < 0.05$.

Results

Sample characteristics are presented in Table 1. There were no significant differences across the groups in terms of age, BMI, sleepiness, depressed mood, fatigue, and apnea severity at baseline.

Using normative scores, we examined how many patients with OSA showed neuropsychological impairment; T-scores less than 40 were designated as “impaired”, as scores below this level are well below the mean and median normative scores. Patients in our sample showed diffuse small levels of cognitive impairments with substantial impairments in terms of verbal learning and memory at baseline, (Table 2). Impaired subjects were identified frequently by the Hopkin’s Verbal Learning Test-learning (44%) and delayed recall (47%).

Table 3 summarizes the Pearson correlation coefficients between baseline GDS and the psychological variables and sleep characteristics. The baseline GDS was not significantly associated with any of the variables of interest. Demographic variables showed no correlation with GDS.

To verify the effectiveness of the blinding process, before discharge from the study, the subjects were asked what they thought their treatment assignment was. 38% of subjects had no opinion as to their therapy assignment, 17% guessed incorrectly, and 45% of subjects correctly guessed their treatment assignment at completion of the study.

After 3-weeks of treatment, AHI and ODI decreased significantly in the therapeutic CPAP group, whereas the placebo group did not show any significant improvement (time $\times$ treatment effect AHI $p=0.004$ and ODI $p<0.001$). The two arms of the study showed different compliance levels ($p<0.001$): Placebo-CPAP patients used the treatment 6.94 ± 1.4 h/night (range = 4.6-10.2); active CPAP patients used the treatment 5.04 ± 0.9 h/night (range = 3.4-7.2).

Tables 4 and 5 show pretreatment and posttreatment means for the neuropsychological test raw and T-scores (respectively) in the 2 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—Word Ratio, Brief Visuospatial Memory-Total Recall, and Word Fluency—Total scores. However, when examining Time $\times$ Treatment interactions, no neuropsychological test showed significant improvement specific to CPAP treatment (Table 4).

When we repeated the analysis with T-scores, significant changes over time, regardless of treatment, were observed for Digit Symbol—Number Correct, Digit Vigilance—Time, Stroop Color—Word Ratio. When examining Time $\times$ Treatment interactions, only Stroop Color-Number correct ($p = 0.048$) showed significant improvement specific to CPAP treatment. However, there was no significant Time $\times$ Treatment interaction for the GDS (table 5).

Discussion

Overview

This paper demonstrated the kinds of experimental design considerations necessary for designing studies related to cognitive effects of sleep disorders. The sleep apnea patients in this study manifested diffuse neuropsychological impairments prior to treatment, but these impairments were evident across the entire range of measures of apnea severity; i.e. AHI was not associated with the degree of cognitive impairments. We did not find a significant change in general cognitive functioning (GDS score) after 3-week CPAP treatment. However, one specific cognitive test (i.e., Stroop color, number correct) demonstrated a specific improvement with 3-weeks CPAP treatment as compared with placebo treatment.

Extent of neurocognitive impairments

The diffuse neurocognitive impairments that we identified prior to treatment are somewhat at odds with findings of a meta-analysis, which found that neuropsychological deficits in untreated apneics were particularly evident in vigilance and executive function, whereas deficits in verbal and intellectual functioning were minimal⁸. It is intriguing that our sample demonstrated considerable diffuse cognitive deficits, even in this group of untreated OSA patients who had little medical comorbidity. In our prior studies, we also observed that the untreated OSA patients showed general cognitive impairment prior to treatment. Thus, this observation replicates our earlier observations in another group of apneic patients¹⁷.

Effect of CPAP

Many of the cognitive impairments improved (i.e., speed of information processing, vigilance, executive function, and visuospatial memory), but there were no time-by-treatment effects using the raw scores of each neuropsychological test. When we used demographically adjusted T-scores, only 3 out of 15 neuropsychological tests were improved over time, and those 3 tests were related to speed of information processing. Moreover, in the analysis with T-scores, we found only one significant time-by-treatment effect in Stroop Color test (number correct). The difference in findings between raw scores and T-scores suggests that T-scores allow us to detect a treatment effect that gets lost when looking at raw score alone. By making demographic adjustments of gender, age, education and ethnicity, T-scores allow one to account for differences in test performance that may be associated with these non-clinical patient characteristics.

In previous randomized controlled studies, only some neurocognitive impairments were improved after CPAP treatment. Barbe and colleagues reported no change after 6-weeks of CPAP treatment,¹⁴ Bardwell and colleagues reported improvement in general cognitive functioning with no specific changes in any specific cognitive domains after 1 week CPAP treatment¹⁶. More recently, Lim and colleagues did not find a significant difference for the effect on global deficits among patients receiving 2 weeks of CPAP treatment, nocturnal oxygen supplementation, or placebo-CPAP¹⁷. How can we understand the overall lack of improvement in cognitive functioning after CPAP? Obvious design features that might account for this are: inadequate sample size, unique sample characteristics, the length of the clinical trial (3 weeks), inadequate or insufficiently sensitive neuropsychological measures³⁶.

Sample size

Given that our sample size was relatively small (i.e., total sample of 38 patients), lack of a significant effect may reflect limited statistical power. On the other hand, the p value of the interaction terms was not even close to significant (i.e., it exceeded $p>0.15$) in the bulk of the comparisons. In particular, across the 15 neuropsychological tests, we observed effect-sizes ranging from 0.01 to 0.47 when comparing the treatment versus placebo arms, with the majority (8 of 15) of neuropsychological tests exhibiting effect-sizes between 0.2 and 0.3. Sample-sizes of 185 to 412 per treatment arm would be needed to detect effect-sizes of this magnitude with 80% power, assuming a significance level of 0.05. Setting $\alpha=0.0033$ corresponding to a Bonferroni correction for 15 neuropsychological tests would require 334 to 750 participants per treatment arm. Clearly, if 3-weeks of CPAP has beneficial effects on cognitive functioning, those effects must be relatively minor in nature, and larger sample-sizes would be required to discern such effects.

Sample characteristics

A larger sample size might also facilitate subgroup analyses. For instance, it is possible that patients with certain characteristics such as more medical comorbidity or more extensive cognitive impairments prior to treatment might show more therapeutic effect of CPAP treatment.

Duration of intervention

A longer treatment interval may be necessary to demonstrate specific effects of CPAP. Nonetheless, in other work we demonstrated that the 3-week intervention was sufficient to lead to highly significant and positive specific effects on fatigue³⁵. It is possible that cognitive impairments may require more time on treatment in order to demonstrate positive effects of CPAP (e.g, 6 months).

Neuropsychological assessment battery

Although we employed a broad-based cognitive assessment used extensively for measuring various domains of cognitive function, further research is required to determine whether other neuropsychological tests may have more sensitivity to subtle changes after CPAP treatment.

Type of placebo intervention

It is possible that placebo intervention without wearing the mask might get different results. Contrary to our current study results, previous reports showed that significant improvements were observed in vigilance, verbal fluency, and speed of information processing tasks in 4-8 weeks of CPAP treatment compared with oral placebo (tablet)³⁷⁻³⁹.

Conclusion

Although it is clear that CPAP improves respiratory disturbances, our work suggests that double blind placebo trials are necessary to establish specific treatment benefits of CPAP on neuropsychological functioning.

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Table 1
Baseline Demographic and Sleep Data in Total Subjects (Mean±SD)

	Placebo (N=21)	CPAP(N=17)	P value
Age, y	48.3±9.6	49.0±9.8	0.823
BMI, Kg/m ²	28.7±4.0	28.4±3.3	0.798
Years of Education, y	15.5±2.2 ^a	16.7±2.1 ^b	0.116
African American	1	2	
Ethnicity White	19	15	0.497
Other	1	0	
ESS	10.2±5.6	7.3±4.5	0.086
CES-D	11.0±7.2	8.9±6.6	0.383
MFSI-sf total	7.1±15.6	2.7±14.1	0.375
AHI (events/hr)	32.6±18.0	28.9±10.2	0.425
ODI (events/hr)	21.6±16.7	20.42±10.6	0.785
Average Oxygen Saturation (%)	95.4±2.2	94.4±1.8	0.158

BMI body mass index; *ESS* Epworth Sleepiness Scale; *CES-D* Center for Epidemiologic Studies Depression Scale; *MFSI-sf* Multidimensional Fatigue Symptom Inventory short form; *AHI* apnea hypopnea index; *ODI* oxygen desaturation index

^aN=19

^bN=15

Table 2
Percentage of Subjects with Impaired Neuropsychological Functioning before Treatment

Neuropsychological Test	% ^a
Digit Symbol, number correct	8.8
Symbol Search, number correct	14.7
Digit Vigilance, time	2.6
Trail Making A, time	14.7
Stroop Color, number correct	23.5
Letter/Number Sequencing	5.9
Digit Span Total	13.2
Digit Vigilance, number errors	23.7
Trail Making B, time	2.9
Stroop Color-Word ratio	14.7
Brief Visuospatial Memory Test-TR	8.8
Hopkins Verbal Learning Test-TR	44.1
Brief Visuospatial Memory Test-DR	5.9
Hopkins Verbal Learning Test-DR	47.1
Word Fluency Total	12.1

TR total recall, *DR* delayed recall

^aPercentage of subjects with < 40 T-score, implying impaired neuropsychological functioning in the tests before treatment (i.e. therapeutic CPAP or Placebo CPAP)

Table 3
Relationship between GDS and sleep variables (N = 38)

Correlation of GDS ^a with:	r	P value
ESS	−0.185	0.265
CES-D	−0.174	0.295
MFSI-sf total	−0.296	0.071
AHI (events/h)	−0.053	0.752
ODI (events/h)	−0.095	0.569
Time at SaO ₂ <90% (min)	0.052	0.756
Sleep stage (%)	Stage 1	−0.172 0.301
	Stage 2	−0.166 0.319
	Slow wave sleep	0.129 0.441
	REM	0.216 0.193

GDS *Global Deficit Scores*; ESS *Epworth Sleepiness Scale*; CES-D *Center for Epidemiologic Studies Depression Scale*; MFSI-sf *Multidimensional Fatigue Symptom Inventory short form*; AHI *apnea hypopnea index*; ODI *oxygen desaturation index*; REM *rapid eye movement sleep*

^a Higher Global Deficit Scores indicate poorer performances.

**
p < 0.05

Table 4
Mean Neuropsychological Test Scores Using Raw Data

Neuropsychological Test	Placebo (N=21)		CPAP (N=17)		P Value ^a	
	Pre	Post	Pre	Post	Time	×Treatment
Digit Symbol, number correct	75.9	80.0	71.8	77.2	<0.001**	0.494
Symbol Search, number correct	34.2	36.2	33.8	36.9	0.004**	0.502
Digit Vigilance, time ^b	373.7	364.8	366.8	346.4	0.025**	0.366
Trail Making A, time ^b	26.3	24.2	26.8	24.7	0.022**	0.942
Stroop Color, number correct	71.2	71.1	72.2	75.1	0.185	0.157
Letter/Number Sequencing	11.5	11.7	11.3	11.1	0.922	0.512
Digit Span Total	18.4	18.9	18.2	19.5	0.099	0.401
Digit Vigilance, number errors ^b	6.1	5.3	9.1	9.5	0.832	0.545
Trail Making B, time ^b	60.0	55.1	63.5	67.0	0.799	0.266
Stroop Color-Word ratio	42.3	45.1	40.5	45.0	0.007**	0.503
Brief Visuospatial Memory Test-TR	26.1	28.9	27.5	29.2	0.010**	0.524
Hopkins Verbal Learning Test-TR	27.1	27.4	26.1	26.0	0.932	0.801
Brief Visuospatial Memory Test-DR	10.5	10.7	10.8	11.2	0.196	0.668
Hopkins Verbal Learning Test-DR	9.5	9.8	9.2	8.8	0.859	0.330
Word Fluency Total	43.5	45.3	47.1	50.7	0.035**	0.494

TR total recall, DR delayed recall

^a P values are listed for effects of time and the time × treatment interaction.

^b Lower scores indicate better performances.

*** p < 0.05

Table 5 Mean Neuropsychological Test Scores Using T-scores

Neuropsychological Test	Placebo (n=21)				P Value ^a	
	Pre	Post	Pre	Post	Time	×Treatment
Digit Symbol, number correct ^b	51.0	55.0	51.0	55.0	<0.001**	0.962
Symbol Search, number correct ^b	52.0	51.3	54.3	57.5	0.226	0.169
Digit Vigilance, time ^b	51.2	52.4	52.4	56.0	0.015**	0.220
Trail Making A, time ^c	50.0	51.1	53.0	55.0	0.237	0.755
Stroop Color, number correct ^b	46.2	45.3	48.7	53.0	0.261	0.048**
Letter/Number Sequencing	51.2	52.4	53.0	52.0	0.982	0.334
Digit Span Total	51.0	52.0	50.0	53.0	0.108	0.489
Digit Vigilance, number errors ^c	48.4	50.2	46.3	46.0	0.643	0.488
Trail Making B, time ^{b, c}	51.3	51.0	53.0	50.0	0.380	0.490
Stroop Color-Word ratio	48.4	52.4	49.0	56.5	<0.001**	0.161
Brief Visuospatial Memory Test-TR	51.0	51.0	53.0	52.0	0.631	0.835
Hopkins Verbal Learning Test-TR	41.3	42.4	37.8	39.5	0.457	0.866
Brief Visuospatial Memory Test-DR	52.0	52.3	55.8	55.6	0.863	0.773
Hopkins Verbal Learning Test-DR	40.8	41.2	38.1	36.0	0.771	0.609
Word Fluency Total ^d	49.3	50.5	54.9	57.1	0.164	0.644
GDS ^e	0.275	0.238	0.349	0.344	0.486	0.594

TR total recall, DR delayed recall

^a P values are listed for effects of time and the time × treatment interaction.

^b N Placebo =19, CPAP=15

^c Higher T-scores indicate better performances.

^d N Placebo=19, CPAP=14

^e Higher Global Deficit Scores indicate poorer performances.

p < 0.05