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Original Article

Neurocognitive function in patients with residual excessive sleepiness from obstructive sleep apnea: a prospective, controlled study

Ksdy S. Werli [a], Leonardo J. Otuyama [a], Paulo H. Bertolucci [b], Camila F. Rizzi [a], Christian Guilleminault [c], Sergio Tufik [a], Dalva Poyares [a,*]

[a] Department of Psychobiology, Universidade Federal de São Paulo, São Paulo, Brazil
[b] Department of Neurology, Universidade Federal de São Paulo, São Paulo, Brazil
[c] Sleep Disorders Center, Stanford University, Stanford, CA, USA

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ABSTRACT

Objective: This study aimed to evaluate neurocognitive function in adult patients with residual excessive sleepiness (RES) after appropriate treatment of obstructive sleep apnea (OSA) with CPAP and good adherence to treatment.
Methods: This was a prospective controlled study. We included patients of both sexes, aged 35–60 years with OSA and an apnea–hypopnea index >20 ev/h, effectively treated with CPAP, but with a residual Epworth Sleepiness Scale score ≥11. The control group consisted of OSA patients adequately treated with CPAP who did not present with excessive sleepiness after treatment. Both groups underwent the following evaluations: polysomnography, multiple sleep latency testing, depression symptoms, and cognitive assessment.
Results: Regarding baseline characteristics, the data were matched for age, years of study, and body mass index. Long-term memory result did not show a significant difference between the two groups (RES group 4.7 ± 2.0; control group 6.5 ± 1.9; $p = 0.08$). The executive functions were the most affected, with alterations in Wisconsin test, number of categories (RES group: 1.6 ± 1.4; control group: 3.0 ± 1.4; $p = 0.01$), and semantic verbal fluency test (RES group: 13.6 ± 3.3; control group: 16.9 ± 4.3; $p = 0.04$).
Conclusion: In summary, the mean depression scale score in the group with residual excessive sleepiness was significantly higher than that in the control group. Patients with residual excessive sleepiness showed impairment of executive functions but no impairments in other cognitive domains.

1. Introduction

Obstructive sleep apnea (OSA) is a sleep respiratory disorder characterized by partial or total obstruction of the airway, which causes arousals, intermittent hypoxemia, and/or hypercapnia. OSA is also associated with cardiovascular consequences and increased mortality [1]. One of the primary and most well-documented daytime symptoms of OSA is excessive daytime sleepiness (EDS), which has an impact on quality of life and may be associated with cognitive and psychological deficits [2].

Continuous positive airway pressure (CPAP) is the gold standard treatment for OSA [3]. Studies show that CPAP is effective in improving EDS in patients with OSA [3,4]. Thus, some patients with OSA continue to experience excessive sleepiness (ES) after treatment with CPAP. Possible confounding factors include low treatment adherence, inadequate titration, insufficient sleep time, the presence of other nondiagnosed sleep disorders, some neuropsychiatric disorders, and the use of sedating and hypnotic medications. However, after the exclusion of these factors, approximately 6% of patients still present with residual excessive sleepiness (RES) [5].

Such RES may be associated with significant declines in psychosocial and cognitive daytime functioning, resulting in a poor quality of life [6]. A recent study from our group showed that effective CPAP treatment in patients with moderate to severe OSA was associated with a 3.59 hours per night significant minimum that was sufficient to increase quality-adjusted life-years [7]. This was also associated with an improvement in EDS and blood pressure levels.

Patients with OSA exhibit deficits in memory, attention, and executive functions [8]. Sleep fragmentation and deprivation associated with EDS have been suggested as fundamental mechanisms in the development of cognitive deficits in OSA, especially with regard to attentional functions [9]. Studies have shown that neuronal damage caused by intermittent hypoxia may affect performance on neuropsychological tests [10] as well as result in a higher scores on scales of depression and anxiety compared with healthy controls and compared with treated OSA patients without RES [6]. Animal studies suggest that exposure to chronic hypoxia may lead to an RES phenotype as a result of possible neuronal damage [11].

* Corresponding author. Department of Psychobiology, Universidade Federal de São Paulo, Rua Napoleão de Barros, 925, 2nd floor – 04024-002, Vila Clementino, São Paulo, SP, Brazil. Fax: +55 11 5572 5092.
E-mail address: poyares@unifesp.br (D. Poyares).

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We hypothesized that patients with RES exhibit cognitive impairments that are related mainly to executive dysfunction compared with patients who experience reduced EDS upon effective treatment with CPAP.

The objective of this prospective study was to compare the cognitive performance of patients with RES with that of patients with OSA who were equally treated with CPAP and who did not present with RES.

2. Methods

2.1. Experimental design

This was a prospective, controlled study. Initially, 202 patients were consecutively diagnosed with moderate to severe OSA (AHI > 20). All patients were treated with CPAP. After one year of treatment, 26 patients remained somnolent (ESS ≥ 11); to confirm the presence of EDS, patients were subjected to the Multiple Sleep Latency Test (MSLT). Three patients had two or more sleep-onset rapid eye movement (SOREM) periods in the test and were subsequently diagnosed with narcolepsy; these patients were excluded from the study. The other 23 patients remained in the study and had their CPAP pressures increased by 2 cm H_2O for one month to assess the possibility of insufficient titration. Five patients exhibited improved sleepiness and were not classified as having RES. Initially, 18 patients were included in the RES group; however, one female patient was excluded from the study because of traumatic brain injury, and two more patients were excluded because they were older than 65 years at the time of follow-up.

The study was conducted with 30 patients who were divided into two groups: an RES group (15 patients) and a control group (15 patients with OSA who were adequately treated and not experiencing RES). All patients used CPAP adequately (mean use of >4 hours per night, with a minimum of 70% of the time) and maintained an ESS score ≥11. Fifteen patients without RES were paired with the RES patients based on age and sex to form a control group. Both the RES group and the control group underwent cognitive and psychological evaluation.

The present study is registered at clinicaltrials.gov under the number NCT01590420 and was approved by the Ethics Committee of the Universidade Federal de São Paulo, Brazil, under the number 019441/2014. All patients signed an informed consent form and were treated with CPAP.

2.2. Study population

Inclusion criteria were as follows: age between 30 and 65 years; confirmed diagnosis of OSA with AHI >20; and referred to treatment with CPAP for approximately one year. Patients were classified with RES if ESS was ≥11 after daily CPAP more than 70% of the sleep time or usage >4 hours per night for a minimum of six months.

Exclusion criteria were as follows: neurological or psychiatric disease, chronic use of central nervous system stimulants and/or depressant drugs, other sleep disorders, illiteracy, and visual impairment that was noncorrectable with the use of corrective lenses. All patients underwent a clinical evaluation before enrollment in the study. The clinical evaluation included general health information (diseases, medications, and pain evaluation) and information regarding education, professional level, and medical complications.

2.3. Multiple sleep latency test

All patients included in the study were subjected to the Multiple Sleep Latency Test (MSLT) to confirm EDS and to potentially exclude narcolepsy. The MSLT consists of five 20-minute reports at two-hour intervals. The test is conducted shortly after a night of polysomnography (PSG), with the first report beginning 1.5–3.0 hours after morning awakening. After each report, the patient is encouraged to take a more comfortable position and to try to doze off. The variables monitored include electroencephalography (EEG), electrooculography (EOG) (left and right), electromyography (EMG) (submentonian), and electrocardiography (ECG) [12].

2.4. Diagnostic polysomnography and CPAP titration

As cited in a previous study [7], a PSG was conducted in all patients using the EMBLA system (17 channels, Medicare Natus Medical Devices Neurology, Oakville, Ontario, Canada). The following variables were monitored: EEG (four channels); EOG (two channels); EMG (submentonian and anterior tibial); ECG (modified channel DII); snoring; and body position.

Nasal air flow was monitored through a pressure transducer, and respiratory effort was measured by the use of abdomen and thoracic sensors. Arterial oxygen saturation was recorded using a pulse oximeter (Ohmeda 3700, GE Healthcare, Finland). All PSGs were scheduled following the guidelines of the American Academy of Sleep Medicine (AASM) for sleep studies [13].

A second complete PSG was conducted for CPAP titration purposes. The CPAP titration PSG was considered satisfactory if the respiratory disorder index (apnea, hypopnea, and flow limitation events) was ≤5 events per hour of sleep [14].

2.5. Epworth Sleepiness Scale

Using the Epworth Sleepiness Scale (ESS), patients were instructed to evaluate the chance of dozing in eight routine situations, scored as 0, 1, 2, or 3 (would never doze off, slight, moderate, and high chance of dozing, respectively). The total score varies from 0 to 24; a result greater than 10 suggests clinically relevant EDS [15].

2.6. Beck Depression Inventory

The Beck Depression Inventory (BDI) self-reported scale evaluates depression levels. The questionnaire includes 21 items, and each item receives a score from 0 to 3. The final result varies from 0 to 63, with higher numbers indicating more severe depressive symptoms [16].

2.7. Neuropsychological instruments

2.7.1. Wisconsin Card Sorting Test

This test evaluates the following functions: formation of concepts and problem solving, mental flexibility, abstraction-reasoning, and strategizing [17]. Outcome variables are the number of categories completed and perseverative errors.

2.7.2. Digit Span

The Digit Span measures cognitive abilities of attention, working memory (central executive), and inhibition, especially for reverse order [18]. The outcome variable is number of digits recalled.

2.7.3. Stroop Color-Word Test

The Stroop Color-Word Test measures selective and focused attention, cognitive flexibility, and inhibition. The variables studied were the number of "hits" for each card and the gross score of color-word interferences [19]. The outcome variable was time to complete the task.

2.7.4. Trail-Making Test A

The Trail-Making Test (TMT) A measures attention and visual search abilities. Volunteers are instructed to draw lines that connect numbers in the correct sequence as rapidly as possible [20]. The

outcome variables are time to complete the task and number of errors.

2.7.5. Trail-Making Test B

The Trail-Making Test (TMT) B evaluates processing speed, inhibition, praxes, and cognitive flexibility, in addition to involving visual and motor planning [20]. The outcome variable is time to complete the task.

2.7.6. Rey Auditory Verbal Learning Test

The Rey Auditory Verbal Learning Test (RAVLT) measures immediate memory, learning efficiency, interference effects, and recall after short and long periods [21]. Outcome variables are the number of words immediately recalled (one to five) and number of words recalled after 30 minutes.

2.7.7. Verbal Fluency and Categories

Verbal Fluency and Categories (FAS Test) evaluates the capacity of evoking words (under delimited conditions) and problem-solving strategies [22]. The outcome variable is the number of words remembered.

2.7.8. Codes

Codes measures psychomotor performance, sustained attention, selective attention, and components of perceptual organization [18]. The outcome variable is one point for each symbol drawn.

2.8. Therapy with CPAP

CPAP with a heated humidifier was prescribed by the sleep specialist and administered by a trained respiratory physiotherapist to all patients included in this study. A clinical evaluation was performed, and CPAP use was assessed during the first week and after one, six, and 12 months of treatment. Arterial pressure was assessed at baseline, six months, and one year after the initiation of CPAP. Treatment compliance was considered adequate if CPAP was used for a minimum of four hours per night at least 70% of the time, as evaluated in the CPAP report [7].

2.9. Procedures and application of cognitive tests

All patients underwent the same cognitive tests, maintaining the same order of application and the same timing. The following order of tests was used: RAVLT, Digit Span, Codes, Stroop, TMT A and TMT B, FAS Fluency, FAS Categories, Wisconsin, BDI, and RAVLT (30-minute latency). The administration time of the tests was always from 10:00 to 11:00 or from 11:00 to 12:00. The duration of the testing was 45–60 minutes.

2.10. Statistical analyses

Results are presented as means and standard deviations, with frequency variables presented as percentages. To check for normality of data, the Kolmogorov–Smirnov test was used. The Mann–Whitney *U* test was applied to compare continuous variables between the two groups for polysomnography data and scores on the BDI. Frequency variables were analyzed using the Fisher exact or χ^2 test. Analysis of covariance was used to compare the results of the cognitive tests, using BDI scores and the presence of hypertension as covariates in view of the strong association between hypertension and possible cognitive deficits that has been reported. The Spearman correlation test was performed between the BDI and cognitive tests, and between the hours of CPAP use and both cognitive variables and depression. The significance level adopted was $p < 0.05$.

3. Results

3.1. General results

All patients and controls reported proper sleep according to their routine the week before the tests and met the minimum criteria for the use of CPAP (Table 1). We also controlled for variables such as age, years of education, and body mass index (BMI). The groups did not differ with respect to age, sex, years of education, hours, and length of CPAP use (years), or average CPAP pressure.

There was no significant difference in the ESS at baseline; a significance difference in ESS scores was found only at the time of evaluation (RES group: 15.0 ± 2.5; control group: 4.8 ± 2.5; $p = 0.01$); as expected, the RES group was sleepier than the control group after one year of treatment with CPAP, as shown in Table 1. There were no reports of significant adverse events in the groups of patients with OSA treated with CPAP. There were, however, reports of nonrelevant upper-airway dryness, which did not interfere with adherence to treatment and resolved with topical interventions (n = 10 of 30 patients). In the psychological evaluation, BDI scores were significantly higher among the patients with sleepiness when compared to the control group (RES group: 13.6 ± 9; control group: 6.4 ± 5.5; $p = 0.04$).

3.2. Polysomnography results

The PSG and MSLT data are available in Table 2. Patients with more than two onsets of rapid eye movement (REM) sleep during the MSLT recordings were not included in Table 2, as narcolepsy was

Table 1
Baseline characteristics of study population.

Characteristic	Control group ($n = 15$)	RES group ($n = 15$)	*p*
Age (year)	51.8 ± 8.2	51.0 ± 8.4	0.52
Sex (male)	11	8	0.35
Body mass index	33.4 ± 4.4	33.5 ± 5.6	0.68
Hypertension (%)	40	71.5	0.08
Diabetes (%)	6.7	21.4	0.24
Education (year)	11 ± 4.2	9.3 ± 4.1	0.22
CPAP use (year)	1.9 ± 0.5	2 ± 0.6	0.63
% > 4 hours of daily CPAP use	90.1 ± 9.3	86.5 ± 8.0	0.06
CPAP mean use (h)	6.4 ± 0.8	5.8 ± 0.9	0.09
CPAP mean pressure (cm H_2O)	10.5 ± 2.1	10.5 ± 3.3	0.94
Baseline ESS score	15.1 ± 5.2	15.7 ± 3.1	0.82
One-year ESS score	4.8 ± 2.5	15 ± 2.5*	0.01
Depression symptoms scale, BDI	6.4 ± 5.5	13.6 ± 9*	0.04

BDI, Beck Depression Inventory; ESS, Epworth Sleepiness Scale.
Mann–Whitney *U* test.
* $p < 0.05$.

Table 2
Baseline PSG and MSLT data in study population.

	Control group ($n = 15$)	RES group ($n = 15$)	*p*
AHI	52.30 ± 20.44	56.18 ± 27.55	0.69
RDI	56.7 ± 31.8	71.3 ± 28.4	0.50
Mean SaO_2	95.19 ± 2.63	93.58 ± 2.93	0.17
N1 (%)	10.63 ± 8.1	12.20 ± 12.89	0.71
N2 (%)	58.04 ± 18.65	62.80 ± 16.81	0.51
N3 (%)	18.73 ± 8.51	12.06 ± 4.78	0.09
REM (%)	18.9 ± 6.73	14.6 ± 4.64	0.17
TST (min)	327.60 ± 49.01	360.84 ± 42.28	0.07
Sleep efficiency (%)	84.62 ± 7.53	84.98 ± 10.51	0.92
MSLT (mean sleep latency, min)	9.4 ± 2.7	2.9 ± 2.34*	0.001

AHI, apnea–hypopnea index); MSLT, Multiple Sleep Latency Test; PSG, polysomnography; RDI, respiratory disturbance index; REM, rapid eye movement; TST, total sleep time.
* $p < 0.05$.

an exclusion criterion. There was no significant difference between the groups in relation to the parameters recorded in PSG at baseline. However, the MSLT, as expected, showed a higher degree of sleepiness in the RES group (mean sleep latency, RES group: 2.9 ± 2.34 minutes; control group: 9.4 ± 2.7 minutes; $p = 0.001$).

3.3. Neurocognitive results

The measures of attentional functions showed no significant differences between the groups. Regarding memory measures, there were also no significant differences between the groups after controlling for hypertension (Table 2). With regard to measures of executive functions, differences emerged in the Wisconsin categories (RES: 1.6 ± 1.4; control: 3 ± 1.4; $p = 0.04$), the Wisconsin perseverative errors (RES: 23.9 ± 9.3; control: 10.5 ± 8.6; $p = 0.01$), and the categorical FAS (RES: 13.2 ± 3.3; control: 16.9 ± 4.3; $p = 0.04$). Patients with RES performed more poorly on executive tests when compared to the control group, as shown in Table 3, but showed no changes in other functions, including learning ability, attention, or memory.

3.4. Correlation between depression and cognitive tests

Because depression has been cited as a potential explanatory variable for cognitive impairment and excessive sleepiness, we evaluated the correlation between several pairs of tests: BDI and the Wisconsin test ($r = 0.18$; $p = 0.34$); BDI and FAS fluency ($r = –0.54$; $p = 0.002$); BDI and RAVLT ($r = –0.20$; $p = 0.27$); and BDI and Codes ($r = –0.26$; $p = 0.15$).

The only significant correlation that emerged from these correlations was between performance on the verbal fluency test and the depression scores.

Table 3
Neurocognitive variables in study population.

Tests	Control group ($n = 15$)	RES group ($n = 15$)	p
Attentional measures			
TMT A	40.4 ± 14.3	47.5 ± 21.2	0.45
TMT A-B	51 ± 20.9	74.9 ± 57.9	0.29
TMT errors B	2.0 ± 3.4	4.5 ± 5.2	0.22
Forward digit span	7.8 ± 2.9	6.5 ± 1.8	0.24
Stroop colors C-B	23.4 ± 6.3	26.5 ± 6.9	0.19
Codes	51.3 ± 16.4	38.2 ± 15.9	0.10
Codes errors	1.6 ± 2.1	1.3 ± 1.3	0.98
Memory measures			
RAVLT1	5.2 ± 1.3	5.0 ± 1.1	0.52
RAVLT2	6.9 ± 1.3	6.7 ± 1.7	0.25
RAVLT3	7.5 ± 2.2	7.0 ± 1.3	0.58
RAVLT4	9.0 ± 2.8	8.5 ± 1.5	0.71
RAVLT5	9.4 ± 3.4	9.2 ± 1.8	0.95
RAVLT6	7.2 ± 2.1	6.3 ± 1.4	0.50
RAVLT (list interference)	4.3 ± 1.7	3.8 ± 0.9	0.18
RAVLT (after 30 min)	6.5 ± 1.9	4.7 ± 2.0	0.08
RAVLT (total)	40.8 ± 14.1	37.4 ± 7.0	0.64
Executive functions measure			
Wisconsin (categories)	3.4 ± 1.4	1.6 ± 1.4*	0.04
Wisconsin (perseverative errors)	10.5 ± 8.6	23.9 ± 9.3*	0.01
Fluency animals	16.9 ± 4.3	13.2 ± 3.3*	0.04
FAS (F)	11.8 ± 4.5	12.0 ± 3.1	0.60
FAS (A)	10.5 ± 3.3	8.2 ± 3.5	0.14
FAS (S)	11.3 ± 4.3	8.6 ± 3.6	0.09
FAS (total)	30.7 ± 7.32	25.5 ± 5.3	0.21
TMT B	93.3 ± 24.6	120.0 ± 76.3	0.35
Stroop colors and words	36.0 ± 10.5	42.4 ± 12.2	0.22
Stroop errors C	0.2 ± 0.5	2.6 ± 4.6	0.08
Reverse digit span	4.8 ± 2.1	4.6 ± 2.6	0.61

FAS, Verbal Fluency Test; RAVLT, Rey Auditory Verbal Learning Test.
Analysis of covariance (controlled for hypertension).
* $p < 0.05$.

3.5. Correlation between hours of CPAP use and depression

A significant moderate correlation was found between BDI scores and hours of CPAP use ($r = –0.42$; $p = 0.83$).

3.6. Correlation between hours of CPAP use and cognitive tests

There was no significant difference between hours of CPAP use and cognitive tests versus the Wisconsin test ($r = 0.28$; $p = 0.15$); versus verbal fluency ($r = 0.36$; $p = 0.09$); and versus perseverative errors ($r = 0.28$; $p = 0.89$).

4. Discussion

This study was designed prospectively wherein 202 patients were assessed and effectively treated for OSA. Of these, 15 patients were classified as experiencing RES that was not better accounted for by another sleep disorder. We compared their cognitive performance with 15 matched controls that had no RES after CPAP treatment. Our main result was the demonstration of significant cognitive impairment in the RES group after CPAP treatment, with executive functions and depression scores being the most affected variables.

The pertinent literature is still controversial: in some studies, OSA patients experience impaired executive function as the most common cognitive changes, whereas other studies point to attentional difficulties [23]. In addition, cognitive skills in people with OSA can be affected for a variety of reasons, including nocturnal hypoxemia, sleep fragmentation, daytime sleepiness, and cardiovascular consequences, (with hypertension among them) [24,25].

Because OSA has been associated with cardiovascular conditions, and considering that such conditions can be positively related to cognitive decline [26], it has become important to control for cardiovascular comorbidities, mainly hypertension. Some studies have shown that hypertension in middle age is associated with higher cognitive dysfunction [27]. However, the temporal relationship between hypertension and cognitive deficits is not clear [26].

4.1. OSA and attention

Psychomotor speed and sustained attention were assessed by the Digit Span test, part of the battery of Wechsler Adult Intelligence Scale (WAIS) tests, and did not differ between groups. Psychomotor speed and sustained attention may be impaired in OSA patients compared with healthy controls on tests assessing attention, psychomotor speed, and memory functions [28], the latter of which is the domain found to be the most improved after treatment with CPAP [29].

4.2. Executive functions

In our study, executive functioning was impaired in the group with RES. Impaired executive function reflects problems with the handling of information, inadequate planning, judgment, decision making, inflexibility, impulsivity, and difficulty maintaining motivation [30]. These neurocognitive problems may influence the daily operations and professional performance of the individual. In the present study, we evaluated these functions through the Stroop C, verbal fluency, TMT B, and Wisconsin measures; however, only the Wisconsin and the verbal fluency tests were sensitive enough to identify such dysfunction.

The Wisconsin test has been one of the most sensitive instruments for detecting and evaluating executive functions. Several classic studies have reported on the sensitivity of the Wisconsin test to identify frontal lobe lesions [17]. Another instrument that can evaluate executive functions is the verbal fluency test, which detects mainly

losses related to strategy and judgment and is also directly related to the frontal lobe [22]. In our study, we observed that RES patients had difficulty with strategizing, which may indicate possible frontal lobe impairment, compared to the control group.

Indeed, executive dysfunction can be explained by capacity-of-attention deficit, slow processing speed, and impaired short-term memory, perhaps influenced by drowsiness [9,31]. Thus, executive functions may be impaired in patients with OSA [31–33], but studies on improvements of these functions after CPAP use remain controversial. CPAP has been reported to improve executive deficits [30], and a review conducted by Aloia et al. [29] showed that attention/vigilance improved after treatment of OSA in most studies. However, changes in global functioning, improved memory, and executive functioning occurred in only about half of these studies, and a study by Saunamäki and Jehkonen [34] suggested that executive function deficits, such as deficits in working memory, can persist after treatment with CPAP. We cannot answer this question because we did not assess cognition at baseline. Our control group, which was successfully treated with CPAP, did not show evidence of executive functioning impairment, whereas the RES group did after one year of effective CPAP treatment.

One study evaluating executive functions in patients with RES did not find changes in neurocognitive measures when compared to a control group [6], but the cognitive assessment in that study was not its main objective. Therefore, it is known that the excessive sleepiness before treatment, fatigue, and changes in attentional functions are symptoms experienced by patients with OSA, and that sleepiness can significantly influence quality of life and can lead to psychological and cognitive problems [2].

4.3. OSA and memory

Other cognitive functions that did differ significantly between the groups were memory and learning. The evaluation of these domains in this study were performed using the RAVLT, which is an instrument that has the ability to assess memory by comparing the number of words learned through immediate recall and subsequent recall [21]. Memory refers to the ability of an individual to receive information from the outside world, to mentally store this information, and to recall it back into consciousness [19,35]. Long-term memory refers to the acquisition and consolidation of new information – that is, learning – and reflects the requirement that an individual is able to recall the information after some time. Memory, attention, and learning have been widely reported cognitive problems in patients with OSA [36]. Memory deficits in OSA patients have been associated with low levels of oxyhemoglobin saturation [37].

Some studies suggest that OSA patients have a significantly poorer performance on tests of verbal and visual memory when compared to healthy controls [38]. OSA patients report more memory complaints when compared to controls, with a trend toward a higher percentage of sleepiness in patients with RES, per a study by Vernet et al. [6].

The preexisting literature suggests that individuals with OSA may have deficiencies in some, but not at all, aspects of memory [36,39]. Patients with OSA and RES therefore have less information storage capacity when compared to treated OSA patients who are lacking residual symptoms (ie, a control group). However, upon controlling for hypertension, this significant effect disappears. The fact that OSA/RES patients remembered few words after 30 minutes may be related to difficulties in strategy, again suggesting some loss of executive functions or influence of cardiovascular factors. A prospective controlled study specifically designed to evaluate the role of hypertension and cardiovascular comorbidities on cognition in OSA patients is needed to clarify this issue.

4.4. OSA, depression, and cognition

Another variable reported in the literature that can influence cognitive changes in OSA patients is depression [40]. In our study, the RES group had the highest score on the depression scale compared with the control group. This is in agreement with the study by Vernet et al. [6], which also showed high scores on depression in patients with RES compared to a control group. The relationship between OSA and depression has been the subject of many studies [10]. Studies that found an increased rate of depression in patients with OSA have also found that the prevalence of depression varies: one rate was found to be 17.6%, using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [41].

In our study, depression was able to explain only changes in verbal fluency, but it did not explain other executive function tests. Thus, cognitive changes in patients with RES were not better explained by symptoms of depression. However, we acknowledge that there was no structured clinical evaluation for the diagnosis of depression in our study.

4.5. Limitations of the study

A limitation of this study was the absence of an initial cognitive assessment before treatment with CPAP, which precludes the assessment of the actual cognitive improvement after treatment. Another possible limitation is that the number of individuals evaluated was relatively small.

5. Conclusion

Patients with RES may be at risk for cognitive impairment – namely, mild impairment in executive functions and verbal fluency. This suggests some potential impairment of the frontal lobe when compared with controls. These impairments were partially explained by hypertension and depression scores. However, we acknowledge that patients with RES had some preserved cognitive functions, such as attention span, learning, and long-term visual memory, which involve different brain areas. In conclusion, nightly hours of CPAP use did not influence the cognitive test results.

Authors' contribution

Ksdy S Werli was responsible for study design, data acquisition, analysis and interpretation, and manuscript writing. Camila F Rizzi was responsible for study design, data acquisition and interpretation, and manuscript writing. Leonardo J Otuyama was responsible for data acquisition and interpretation. Paulo H. Bertolucci was responsible for data acquisition and interpretation. Sergio Tufik was responsible for study design and data interpretation. Dalva Poyares was responsible for study design, data interpretation, and manuscript writing.

Conflict of interest

Ksdy S Werli has nothing to disclose, Leonardo J Otuyama has nothing to disclose. Paulo H. Bertolucci has nothing to disclose. Camila F Rizzi is an employee at Philips. Sergio Tufik has nothing to disclose. Dalva Poyares is an associate professor at Universidade Federal de São Paulo, she has also done consultancy for EMS, Sanofi-Aventis, and Libbs Pharmaceuticals, developing and delivering educational presentations, outside of the submitted work.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2016.06.028.

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