

Sleep abnormalities and memory alterations in obstructive sleep apnea

Alterações do sono e da memória na apnéia obstrutiva do sono

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ABSTRACT

Objectives: Obstructive sleep apnea (OSA) is associated with a variable spectrum of sleep abnormalities and has been connected with memory impairment. The aim of this study was to evaluate the associations between OSA, memory alterations and sleep structure abnormalities. **Methods:** Polysomnography was performed in 20 consecutive patients (12 male, 57.9±5.8 years) with moderate/severe OSA (AHI 35.8±16.7). Daytime somnolence (Epworth Sleepiness Scale, ESS), state of alertness (Karolinska Sleepiness Scale), subjective sleep quality (Pittsburgh Sleep Quality Index, PSQI) and depressive symptoms (Beck Depression Inventory, BDI) were evaluated. Patients were tested before all night polysomnography and a retrieval test was performed in the following morning. Declarative memory was assessed by Verbal Paired Associates from the Wechsler Memory Scale, emotional memory by the exposure to emotional and non-emotional images and procedural memory by the maze test. **Results:** Excessive daytime sleepiness (ESS>10, 55%) and impaired sleep (PSQI>5, 40%) were found. Patients with OSA presented greater neck circumference ($p<0.005$). Procedural memory, as evaluated by the maze test, showed worse retrieval in OSA patients and this was maintained after controlling for age, body mass index and BDI. In subjects with moderate/severe OSA, stage 3 sleep was correlated to the performance in the procedural memory test. **Conclusion:** We show that procedural memory is altered in OSA patients as compared to controls and this alteration is related to stage 3 of non-rapid eye movement sleep. We confirm that recall memory tests after one night sleep are efficacious to examine memory abnormalities in OSA patients.

Keywords: memory, polysomnography, sleep, sleep apnea syndromes.

RESUMO

Objetivos: Apnéia Obstrutiva do Sono (AOS) associa-se com um espectro de alterações do sono e possível redução da memória. O objetivo desse estudo foi avaliar a relação entre a AOS, alterações da memória e anormalidades da estrutura do sono. **Métodos:** Vinte pacientes (12 homens, idade 57,9±5,8 anos) foram estudados com o uso de polissonografia e avaliados quanto à sonolência diurna (Escala de Sonolência de Epworth, ESE), estado de alerta (Escala de Sonolência de Karolinska), qualidade subjetiva do sono (Índice de Qualidade de Sono de Pittsburgh, IQSP) e sintomas depressivos (Inventário de Depressão de Beck, IDB). Casos com AOS moderada/grave (IAH 35,8±16,7) foram submetidos a testes de memória antes da polissonografia de noite inteira e na manhã seguinte, um teste de recuperação foi realizado. Memória declarativa (Pares de Palavras Associadas), memória emocional (Exposição a imagens emocional e não-emocional) e memória de procedimento (Teste do

Labirinto) foram testadas. **Resultados:** Sonolência excessiva diurna (ESE>10, 55%) e má qualidade do sono (IQSP>5, 40%) foram frequentes. Pacientes com AOS apresentaram maior perímetro cervical ($p<0,005$). Memória de procedimento (Teste do Labirinto) mostrou pior recuperação nos pacientes independentemente da idade, índice de massa corporal e sintomas depressivos. Em indivíduos com AOS moderada/grave, o desempenho da memória de procedimento correlacionou-se com o sono N3. **Conclusão:** Os testes de memória após uma noite de sono são eficazes para avaliar alterações da memória em pacientes com AOS. A memória de procedimento está alterada em pacientes com síndrome da AOS e esta alteração relaciona-se com a quantidade de sono N3.

Descritores: memória, polissonografia, sono, síndromes da apnéia do sono.

INTRODUCTION

Sleep is recognized as a physiologic state that performs an essential restorative function and facilitates learning and memory consolidation⁽¹⁾. Obstructive sleep apnea (OSA) is a common disorder which is associated with significant comorbidities, including obesity, hypertension, increased risk for vascular disease, depression and excessive daytime sleepiness. Furthermore, OSA is associated with a variable spectrum of sleep abnormalities and has been previously connected with memory and learning impairment⁽²⁻⁴⁾. Previously, it has been shown that declarative and procedural memory processes are impaired in patients with OSA compared to healthy subjects⁽⁵⁾. However, the mechanisms underlying these cognitive and psychological alterations are still unknown. Memory is a multifaceted task and different sets of memory tests can yield different conclusions. Also, specific sleep alterations, such as change of sleep architecture, arousals and oxygen desaturation can exert different influence in cognitive function.

Structural cerebral changes reported in subjects with OSA support the connection between sleep abnormalities and cognitive dysfunction in those patients^(6,7). For instance, alterations of regional cerebral blood flow in bilateral parahippocampal gyri, right lingual gyrus, pericentral gyrus, and cuneus, found in patients with severe OSA, may partly explain deficits in memory, spatial learning, executive function, and attention⁽⁸⁾. Recently, a study

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about the effects of sleep-wake regulation on the cerebral mechanisms, which focused on the locus ceruleus and the suprachiasmatic nucleus, has proved the direct influence of the homeostatic and circadian control on neural activity⁽⁹⁾.

It should be noted that among OSA patients, only 30% of cases present memory deficits in an initial assessment⁽⁵⁾. This might be a setback for the follow-up evaluation of therapeutic efficacy, as it has been noticed that the best therapeutic results can be checked when patients experience changes in cognitive function at baseline. Beneficial effects of positive pressure ventilation on learning and memory in patients with OSA have been shown⁽¹⁰⁾. However, it is unclear whether the cases that recover are those with cognition similar to controls or those with basal levels different from controls. Ultradian variations of cognitive performance may also occur. Considering such evidence, it is possible that an assessment of memory functioning before and after nocturnal sleep in OSA patients and controls is more appropriate to compare the performance of memory and can generate more information than ratings points into a certain time of day.

The main objectives of this study were to evaluate the effects of OSA on memory retrieval after one night sleep and to determine the contribution of sleep abnormalities to memory alterations.

METHODS

Study Design and participants

This was a case-control study of 20 consecutive patients of both genders referred for polysomnography which were later diagnosed as having moderate/severe OSA (apnea hypopnea index, AHI>15) and 10 healthy subjects, controlled for age and gender. Inclusion criteria were age between 50 and 75 years and the diagnosis of moderate/severe OSA. The diagnosis of sleep apnea was confirmed by two sleep specialists (MD, respiratory physician) in the sleep laboratory. Exclusion criteria were cancer, severe lung, hepatic or renal diseases, previous use of Continuous Positive Airway Pressure (CPAP) and unwillingness to participate in the study. All subjects were free from any medication that might affect sleep or cognition and did not consume alcohol or caffeine ≥ 24 h prior to or during the study. Asymptomatic individuals with low risk for OSA as assessed by the Berlin questionnaire⁽¹¹⁾, recruited from the community, were studied as controls. The protocol was approved by the local research ethics committee and subjects gave informed consent (CEP/HUWC 002.02.07).

Procedures

A purpose-built questionnaire was used to assess habits and comorbidities, such as type 2 diabetes and systemic arterial hypertension. Demographic and anthropometric data including the hip-waist (cm), neck circumference (cm) and body mass index (BMI) were collected. Body mass index was calculated as the ratio between weight (Kg) and squared height (m²).

Daytime somnolence was evaluated by the Epworth Sleepiness Scale (ESS), a questionnaire containing eight items that ask for expectation of dozing in eight hypothetical situations. Epworth Sleepiness Scale score greater than 10 indicates excessive daytime somnolence⁽¹²⁾. State of alertness was evaluated by the Karolinska Sleepiness Scale⁽¹³⁾. Subjective sleep quality was evaluated by the Pittsburgh Sleep Quality Index (PSQI)⁽¹⁴⁾. Pittsburgh Sleep Quality Index has seven components, each one dealing with a major aspect of sleep: 1) subjective quality of sleep; 2) sleep onset latency; 3) sleep duration; 4) sleep efficiency; 5) presence of sleep disturbances; 6) use of hypnotic-sedative medication; and 7) presence of daytime disturbances, as an indication of daytime alertness. Individuals with total PSQI score of six or more were considered poor sleepers⁽¹⁴⁾. Depressive symptoms were evaluated by the Beck Depression Inventory (BDI)⁽¹⁵⁾. Control subjects were assessed by the Berlin questionnaire⁽¹¹⁾. Measures of sleepiness sleep quality and excessive daytime sleepiness were taken regarding the previous 30 days.

Full polysomnography was performed in all patients with recordings from 22:00 to 06:00h. In addition to questionnaires, memory tests were assessed from 7:00 to 8:00 PM prior to sleep (learning session) and at 06:30 to 07:30 AM after sleep (recall session). Declarative memory was assessed by Verbal Paired Associates (VPA) test from the Wechsler Memory Scale⁽¹⁶⁾. The VPA is used instruments for assessing explicit episodic memory. It consist of four pairs of related and four pairs of unrelated words across three study test trials, and a 30-min delayed recall test⁽¹⁷⁾. The emotional memory was evaluated by the exposure to emotional and non-emotional images. During a first session, participants viewed 15 pictures with neutral and emotional content. Thirty minutes after the initial exposure, 45 images were shown, among which 15 had already been presented (first exposure) and the patient indicated which pictures had been seen. After polysomnography, a new exhibition of 45 images were presented, 15 of these images corresponded to those shown in the first exposure and the other 30 corresponded to previously unseen images and patient files which indicated he recognized previously viewed and new pictures. All images are part of the International Affective Picture System⁽¹⁸⁾. Procedural memory was evaluated using the maze test, part of the Wechsler Intelligence Scale. The Maze Test involves the ability of planning and visuo-spatial memory⁽¹⁶⁾.

Polysomnography recording

Polysomnography was performed according to a standard clinical protocol (ALICE V, Respirationics[®]). Monitored variables included: electroencephalogram (C3, C4, O1, O2 referenced to contralateral ear electrodes), bilateral electrooculograms, submental electromyogram (EMG), two-lead electrocardiogram, pulse oximetry, bilateral tibialis EMG and airflow, using a nasal/oral thermocouple. Body position and thoracic and abdominal movements (inductance plethysmography) were also recorded. Sleep staging was performed by 30-s epochs, according to published recommendations⁽¹⁹⁾. Polysomnography-derived parameters

evaluated were AHI, minimum oxygen saturation (SpO_2 min), sleep latency, sleep efficiency, rapid eye movement (REM) sleep latency, amount of REM sleep (% of total sleep time), amount of non-rapid eye movement (NREM) sleep (% of total sleep time) and number of arousals. Hypopnea was defined as a 50% decrease in the sum of thoracic movements lasting 10 seconds followed by a decreased oxygen saturation of at least 4%. As recordings may be misleading in evaluating patients who have a fall in baseline oxygen saturation (SpO_2) during sleep, visual scoring was performed by a trained polysomnographer in all cases. A board certified sleep specialist, blind to diagnosis validated each individual respiratory event and manually made required changes to recorded data. Cases were classified as having moderate/severe OSA ($\text{AHI} \geq 15$) or control group. Intake of sedative medication was not allowed within 48 hours of the investigation. Assessment of subjective overnight sleep quality was taken from patient and care giver.

Statistical Analysis

Data are expressed as means \pm standard deviation (SD) values. Patients were grouped as having or not OSA. Data were examined for normality using the Shapiro-Wilk and for homogeneity of variances with the Levene test. The Fisher's exact test, for categorical variables, Student's *t* test for continuous variables, and Mann-Whitney for non-continuous variables were performed for between groups comparison. Repeated measures multivariate analysis was used to compare memory tests before and after sleep. Pearson correlation test was used to compare delta values of memory performance to structural sleep abnormalities: delta values of memory performance were obtained subtracting results of morning performance from results of the previous night. Statistical Package for the Social Sciences (SPSS- Norusis, 1993) software for Windows was used for analysis. The level of significance was set at $p < 0.05$.

RESULTS

Twenty patients (12 male) with moderate/severe OSA ($\text{AHI} 35.8 \pm 16.7$), aged between 50 and 68 (mean age 57.9 ± 5.8 years) were studied. Excessive daytime sleepiness ($\text{ESS} > 10$) was present in 11 (55%) and impaired sleep ($\text{PSQI} > 5$) in eight (40%) of all OSA cases. Table 1 depicts clinical characteristics of patients with OSA and controls. Age, BMI, hypertension, diabetes, excessive daytime sleepiness were similar in both groups. Patients with OSA presented greater neck circumference ($p = 0.000$). Sleep quality as assessed by the PSQI tended to be worse in OSA patients ($p = 0.07$). BDI scores and the Karolinska sleepiness scale were not different between OSA and control subjects. Obstructive sleep apnea patients presented variable polysomnographic values that are described as follows: sleep latency (Range 2.5-42.0 min; mean 12.8 SD 10.6), REM latency (Range 45-207.5 min; mean 93.9 SD 50.3), REM sleep percent of total sleep time (Range 5.8-32.5; mean 20.1 SD 6.2), N3 sleep percent of total sleep time (Range 0-17.4; mean 7.4 SD 5.6), sleep efficiency (45.1-100.0;

mean 87.7 SD 12.8), AHI (Range 16.7-73.2; mean 35.8 SD 16.7), arousal index (Range 6.4-53.2; mean 27.7 SD 12.1), Minimal SpO_2 (Range 46-90; mean 72.3 SD 14.3).

Table 1. Demographical and clinical characteristics of patients with moderate/severe obstructive sleep apnea and control subjects.

Variables	Controls N=10	AHI \geq 15 N=20	<i>p</i> value
Gender (Male/Female)	3/7	12/8	^b 0.24
Age (y) mean (SD)	56.4 \pm 6.3	57.9 \pm 5.82	^a 0.51
BMI	27.6 \pm 4.0	29.8 \pm 5.21	^a 0.25
Neck circumference (cm)	37.4 \pm 2.6	43.3 \pm 3.58	^a 0.000**
Hypertension	6 (60%)	11 (55%)	^b 1.00
Diabetes	2 (20%)	5 (25%)	^b 1.00
PSQI	4.6 \pm 2.6	7.0 \pm 3.85	^c 0.07
ESS	8.1 \pm 4.1	10.9 \pm 6.60	^c 0.28
Karolinska Scale	5.3 \pm 1.56	5.0 \pm 1.74	^c 0.55
Beck Depression Inventory	3.1 \pm 4.28	6.0 \pm 5.78	^c 0.10

Abbreviations: BMI= Body Mass Index; RLS=Restless Legs Syndrome; PSQI= Pittsburgh Sleep Quality Index; ESS= Epworth Sleepiness Scale. ^aStudent's test; ^bFisher's exact test; ^cMann-Whitney.

Procedural memory as evaluated by the maze test showed worse retrieval in OSA patients (Table 2) which remained significant after controlling for age, BMI and Beck depression scores ($p = 0.2$). In patients with moderate/severe OSA, N3 sleep was correlated to delta results of the maze test ($r = 0.46$, $p = 0.03$). Results of the maze test before and after polysomnography are shown in Figures 1 and 2.

DISCUSSION

This study comparing memory retrieval after one night sleep shows that procedural memory, as evaluated by the maze test, is significantly impaired in moderate/severe OSA patients and these alterations are correlated with N3 sleep abnormalities. These findings corroborate the idea that healthy sleep fosters new memory consolidation. Previously, procedural memory has been shown to be impaired in subjects with insomnia⁽²⁰⁾ and in patients with depression and schizophrenia⁽²¹⁾. However, in those studies, a relationship between memory alterations and specific sleep abnormalities was not investigated. Our data indicate that N3 sleep reduction may produce crucial functional abnormalities in brain circuits relevant for memory. Previously, slow wave (N3) sleep abnormality has been related to memory consolidation in schizophrenia⁽²²⁾.

These results also highlight the importance of assessing memory consolidation using retrieval memory in overnight studies as opposed to cross-sectional evaluations. This approach will help to evaluate effects therapeutic effects and interactions with comorbidities in OSA.

Previously, Genzel et al.⁽²³⁾ studying a small number of subjects reported that declarative memory was not related to the amount of slow wave sleep or REM sleep. Interestingly, in our data, in contrast to the impairment of procedural memory, OSA patients presented declarative memory similar to control subjects⁽²¹⁾. Whether procedur-

Table 2. Results of memory performance tests in the night before (encoding) and in the morning after polysomnography (retest) in patients with moderate/severe OSA and control subjects.

	Controls (N=10)		IAH \geq 15 (N=20)		p value
	Encoding	Retest	Encoding	Retest	
Maze test (s)	34.2 \pm 14.8	24.1 \pm 11.8	31.8 \pm 24.1	40.7 \pm 39.7	<0.005*
Positive pictures	4.9 \pm 0.3	5.0 \pm 0.0	4.7 \pm 0.5	4.8 \pm 0.3	1.00
Negative pictures	5.0 \pm 0.0	4.9 \pm 0.4	4.9 \pm 0.3	4.8 \pm 0.4	0.76
Neutral pictures	4.6 \pm 0.5	4.5 \pm 0.7	4.3 \pm 0.9	4.4 \pm 0.9	0.40
Total pictures	14.5 \pm 0.5	14.5 \pm 0.7	14.0 \pm 1.2	14.1 \pm 1.2	0.76
False alarms pictures	0.5 \pm 0.9	0.6 \pm 1.0	2.9 \pm 2.8	1.95 \pm 2.3	0.10
PAW (IR)	11.8 \pm 2.8	15.9 \pm 4.0	15.1 \pm 2.7	20.0 \pm 3.1	0.44
PAW (DR)	5.9 \pm 1.4	6.8 \pm 1.3	5.8 \pm 1.6	6.9 \pm 1.4	0.64

Abbreviations: PAW (IR) = Paired associated word (Immediate recall); PAW (DR) = Paired associated word (Delayed recall). * Repeated Measures.

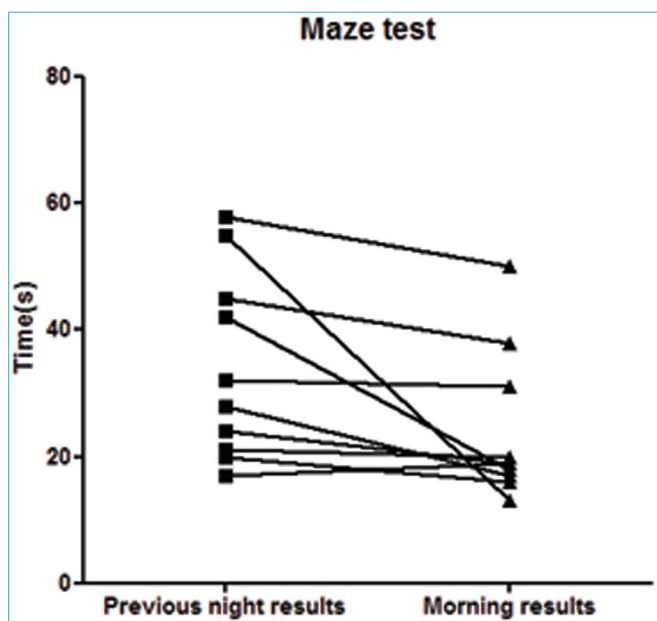


Figure 1. Maze test total time (s) in the following morning is unchanged or decreased when compared to values of the night before polysomnography in control subjects (N=10).

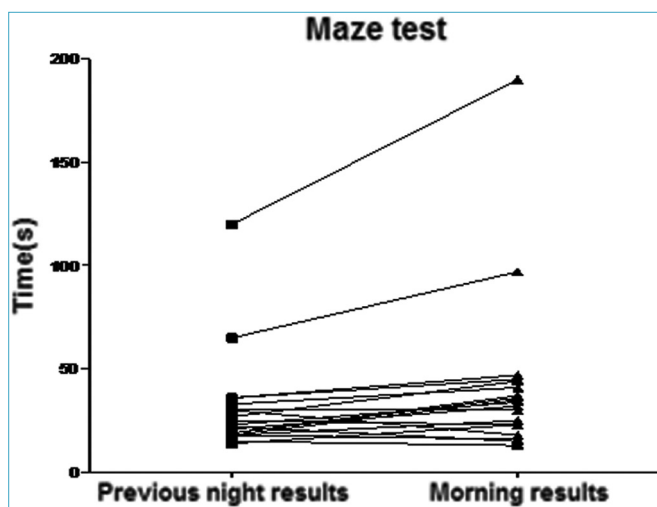


Figure 2. Maze test total time (s) in the following morning are higher when compared to values of the night before polysomnography in moderate/severe OSA subjects (N=20).

al memory is a more sensitive and reliable measure to evaluate memory consolidation still needs to be determined. Procedural memory is involved in storage of memories of

how to do something. This type of complex behavior and function invariably involves frontal cortex in association with structures of the diencephalon. On the other hand, declarative memory is considered a long term memory and involves the recall of either personal experience defined as episodic memory or semantic memory i.e. the meaning of words. It is generally believed that the hippocampus is the main structure involved in declarative memory. Stress and emotional content influence these recall of personal experience and semantic memory: this fact points to the evidence that many structures such as thalamus, hypothalamus and amygdala also participate in declarative memory processes. In corroboration to our findings, in one study of epileptic patients, the evaluation of a declarative (paired-associate word list learning task) and a procedural (sequential finger tapping) task showed that an increase in the amount of slow-wave sleep only improved procedural memory. Those investigators showed that procedural performance enhancement and slow wave sleep were correlated with very low-frequency hippocampal activity⁽²⁴⁾. These evidences are very initial considering the complexity of the brain function and memory.

In our data, despite, the fact that declarative memory was not different in patients with OSA as compared to control, it was found that the delta declarative memory, or the subtraction between overnight and morning results, were correlated to oxygen desaturation. One further step that must be tested is whether improving hypoxemia associated with OSA can modify these findings.

Limitations of this study must be acknowledged. Controls were evaluated only with the Berlin questionnaire and it must be considered that asymptomatic individuals with mild OSA might have been undetected. However, abnormal findings were derived only from patients with OSA syndrome or moderate/severe OSA. Thus, in this study comparisons were obtained from patients with OSA syndrome or moderate/severe OSA and individuals with low risk of apnea or asymptomatic mild OSA which by definition may not be classified as OSA syndrome.

In conclusion, we show that procedural memory consolidation is impaired in OSA patients and this is related to N3 sleep. It remains to be established whether CPAP therapy and the recovery of N3 sleep improve patients

processing capacities. Further studies, particularly using neuroimaging techniques may help to identify specific brain structures involved in memory impairment in OSA.

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