ORIGINAL RESEARCH

DOI: 10.4274/ejgg.galenos.2023.2023-1-2
Eur J Geriatr Gerontol 2023;5(3):246-254

Cognitive Functions in Obstructive Sleep Apnea: Observing the Effects of Continuous Positive Airway Pressure Treatment in Aging Patients

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Abstract

Objective: Obstructive sleep apnea (OSA) is known to have disruptive effects on cognitive functions (CFs) in advanced ages. The aim of this study was to reveal the effect(s) of continuous positive airway pressure (CPAP) treatment on CFs in older patients with OSA.

Materials and Methods: Follow-up comparisons were conducted after 6 months of CPAP treatment in pulmonary medicine departments outpatient clinic of a reference university hospital. Patients were included to study after one-night hospitalization for polysomnographic assessments. All participants underwent a comprehensive neuropsychological evaluation which was repeated after an average of 6 months of regular CPAP treatment. Moderate to severe OSA patients with mean age of 64.9 (n=30; female 56.7%) and control group (CG) with mean age of 67.13 (n=30; female 50%) were included.

Results: OSA patients displayed poorer performance in executive functions and memory as compared to the CG. After the CPAP treatment an improvement was observed on memory; significantly on immediate recall (p=0.044), learning (p=0.017) and recognition (p=0.033) scores of older OSA patients. Also, the clock drawing test scores ameliorated after treatment (p=0.046).

Conclusion: Examining memory functions to its processes showed that OSA may impair learning and free recalling of the recently encoded memory inputs. Follow-up results suggested that the disruption of CFs that may be due to the sleep breathing disorder itself, significantly benefited from 6 months of regular CPAP treatment in older patients with moderate to severe OSA.

Keywords: Sleep breathing disorder, cognition, continuous positive airway pressure, geriatrics, neuropsychological functioning

Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder manifesting with complete or partial upper airway obstruction during sleep (1). This would lead to sleep fragmentations due to apneas, hypopneas (2), and frequent arousals (3). Besides causing various pathophysiological changes (4) OSA is also known to cause deterioration in cognitive functions (5) and pose a risk for progressive cognitive impairment (6).

The prevalence of sleep-related breathing disorders increases with age (7) while age itself is already a confounder for cognitive functioning. Moreover, older adults are reported to be more prone to cognitive decline associated with OSA as compared to their younger (8). Among the reasons for progressive cognitive decline in elderly, OSA is one of the few reversible causes for cognitive impairment (9) but if left untreated, OSA may cause permanent damage on cognition and psychological well-being (10). Despite these versatile impact notifications, OSA studies investigating the effectiveness of CPAP treatment on cognitive

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Received: 05.01.2023 **Accepted:** 12.06.2023

Cite this article as: Büyükgök D, Bingöl Z, Tufan Çinçin A, Kıyan E, Karan MA, Bahat G. Cognitive Functions in Obstructive Sleep Apnea: Observing the Effects of Continuous Positive Airway Pressure Treatment in Aging Patients. Eur J Geriatr Gerontol 2023;5(3):246-254

functions are usually carried out with screening tools (11,12), and follow-up intervals may be relatively short to evaluate the treatment results (13,14). However, the number of studies on the cognitive profiles and treatment responses of patients over 60 years of age with OSA is fewer than with younger participants.

There are increasing number of studies about the relationship between OSA and cognitive impairment (7,8,15). As the previous studies presented, patients with OSA experience difficulties in cognitive functions such as learning new information, using cues that will facilitate retrieval, and making memory-based behaviors such as following an instruction (7,16). The most effective, safe and gold standard treatment for OSA is the practice of "continuous positive airway pressure" (CPAP). As a result of the positive airway pressure, an increase in functional residual capacity is achieved and oxygen saturation during apnea/hypopnea periods is improved. CPAP therapy is expected to result with an improvement at patient's cognitive skills. A meta-analysis of studies, in which treatment efficacy was assessed with neuropsychological tests, reported that the most consistent improvement after CPAP therapy was in the area of attention; i.e., processing speed, memory, working memory, verbal fluency, and visuo-spatial structuring skills (17). A few detailed cognitive evaluations indicating the effectiveness of CPAP therapy also revealed improvement in memory (18,19); sustained attention (20) and executive functions (5,19).

The aim of our study was to reveal the possible effects of OSA on cognition in a sample of patients with moderate to severe OSA and the impact of CPAP treatment with 6 months of follow-up. Since the number of studies with detailed cognitive test battery was limited, we used a comprehensive neuropsychological evaluation for this follow-up study. The significant contribution of this study would indicate that adverse effects of OSA on cognition can be ameliorated with CPAP treatment even in patients above 60 years of age.

Materials and Methods

Participants

We recruited patients among those admitted to pulmonary medicine department's outpatient clinic of Istanbul University Istanbul Faculty of Medicine. Patients, who were diagnosed with moderate to severe OSA via full-night polysomnography (PSG) and subsequently prescribed CPAP treatment, were invited to participate. Thirty-three patients diagnosed with OSA participated in the study (Figure 1). One of the patients was excluded, because the low educational level caused a missing value above 5% in cognitive tests. Although recommended, two of the patients refused to use CPAP device, thus their data were also excluded from to the analysis. Consequently, 30 patients (n=30, f/m =17/13, mean age =65.56± 4.87) diagnosed with moderate to severe OSA with full-night polysomnography were included. Considering the International Classification of Sleep Disorders (2014) inclusion criteria for patient group were having a clinical OSA profile, an apnea-hypopnea index (AHI) ≥5/h and the presence of clinical symptoms or AHI ≥15/h without any symptoms. We excluded patients who were already under positive airway pressure treatment and/or oxygenation therapy, using drugs affecting central nervous system (e.g., anticonvulsants, antipsychotics, benzodiazepines), having any malignancy and history of unstable severe cardiopulmonary disease (e.g., acute myocardial infarction, heart failure), having any kind of developmental disability, neurodegenerative, and neuromuscular diseases. Baseline cognitive and psychological assessments of the OSA patient group were done 2 to 3 days after PSG. Sixteen of the patients with OSA attended the cognitive assessment after treatment and comprised our follow-up group.

Healthy control participants were recruited among patient relatives by using call-boards of the clinics in our hospital (Figure 1). Control group (CG) consisted of volunteered participants who did not report sleep-breathing disorder after a semi-structured medical interview including the Epworth Sleepiness Scale (ESS) (21). Age and education matched participants with Mini Mental State Examination (MMSE) (22) ≥24, Geriatric Depression Scale (GDS) (23) ≤14 and ESS ≤10 was included. We excluded volunteered participants from CG who had sleep complaints, chronic sleep deprivation, chronic use of sedative drugs or alcohol, any malignancy and history of unstable severe cardiopulmonary disease, and any kind of neurological diseases. Participants of CG underwent comprehensive neuropsychological assessment.

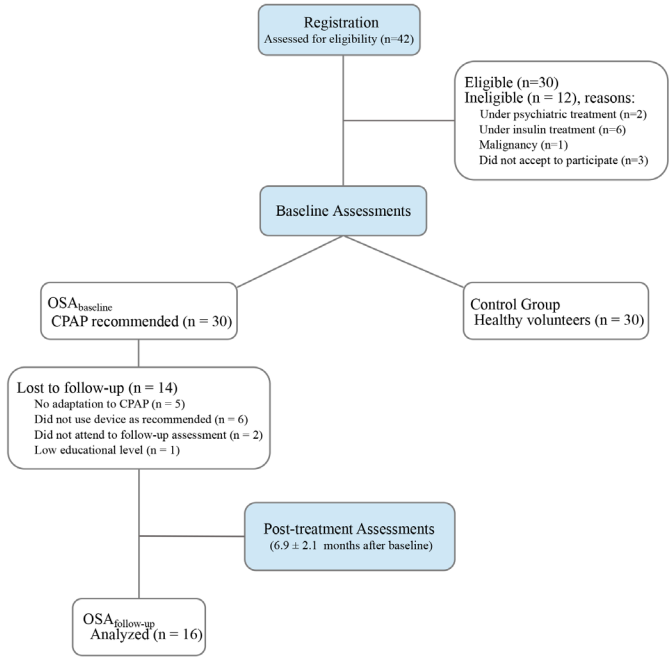

Figure 1. Flow diagram of subjects participating through each stage of the study

Usage of CPAP at least 5 days a week, at least 4 hours a day was accepted as device adaptation (regular CPAP use) (24). Patients using CPAP device minimum of 3 months per 6 months follow-up comprised our follow-up sample. The participants were questioned monthly about the use of CPAP by phone calls. Patients were invited for post-treatment evaluation at 6 months and the data of participants who used CPAP for at least 3 months (within the effective and sufficient time previously reported in this paper) were included. All procedures performed in this study involving human participants were in accordance with the ethical standards of İstanbul University, İstanbul Faculty of Medicine Ethics Committee for Clinical Research and with the Helsinki Declaration (no: 2023-1782132).

Measurements

Polysomnography and Sleep Assessments

OSA diagnoses of the patients were determined after full-night polysomnography (PSG) using the Compumedics E device in Sleep Laboratory of İstanbul University, İstanbul Faculty of Medicine. Sleep stages and respiratory events were scored according to the American Association of Sleep Medicine 2012 guidelines (25). Apnea was defined as a cessation of airflow ≥90% compared with baseline for ≥10 seconds while there was evidence of persistent respiratory effort. Hypopnea was defined as an amplitude reduction of ≥30% in airflow lasting for ≥10 seconds that was associated with an oxygen desaturation of ≥3% or with arousal. Polysomnography records were scored by a trained technician. OSA was diagnosed if the apnea-hypopnea index (AHI) was ≥5/h and the presence of clinical symptoms or AHI ≥15/h without any symptoms. The OSA severity was graded as mild (AHI 5-14/h), moderate (AHI 15-29/h), or severe (AHI ≥30/h). Oxygen saturation level was also recorded. The oxygen desaturation index (ODI) indicates the count of decline of the blood oxygen level below baseline per one hour. Measurements were taken during polysomnography by using a finger oximeter. The CPAP titration study was performed in the sleep laboratory. The pressure correcting apneas and hypopneas was determined to the appropriate pressure for each patient.

The body mass index (BMI) was calculated using Khosla and Lowe's formula [weight (kg)/height^2(m^2)] (26). ESS was filled by the participants and the ESS score of >10 was used as a cut-off value for excessive daytime sleepiness (27).

Neuropsychological Evaluation

Cognitive functions refer to mental processes such as attention, language, memory, visuo-spatial abilities and executive functions. In this study; digit span (forward) (28) was used to evaluate attention and Trail Making Test form A (TMT-A) (29) was used to asses psychomotor speed. Word fluency test, Stroop test (30), Trail Making Test form B (TMT-B) (29), digit span (backwards) (28) and Clock Drawing Test (CDT) were applied to evaluate executive functions. CDT was scored based on the 5-point Shulman scoring system (31). In order to make sure that the scorings of CDT between the pre- and post-treatment measurements was not rater-biased, the drawings were re-scored by a geriatric psychiatrist who was blinded to the study. Word fluency test was both applied with semantic (naming animals) and phonemic categories (words starting with letters K, A, S) for one minute, each. Logical memory subtest of Wechsler Memory Scale-Revised (WMS-R), and California Verbal Learning Test (CVLT) (32) were applied to evaluate memory functions. Baseline cognitive and psychological assessments of the OSA patients were performed 2 to 3 days after PSG.

Statistics

Statistical analyses were performed using IBM SPSS Statistics 21. After assessing distribution characteristics of data with Shapiro-Wilk test, non-parametric statistical analyses were carried out. Mann-Whitney U test was used to evaluate differences between groups' socio-demographic variables, cognitive tests, and psychological scales. For the follow-up comparisons, Wilcoxon Signed-rank test was used. All analyses were run with raw scores; the only exception was the Logical Memory subtest of WMS-R. This test has two alternative forms that include different number of items. Thus, in order to compare results transformed Z-scores of the logical memory subtest were used. Severity effect of OSA on cognitive tests was examined with one-way analysis of variance on ranks (Kruskal-Wallis H test). To study possible associations between sleep assessments and cognitive tests, we used correlation analysis and the results will be given in Spearman's rank correlation coefficients (r_s). Two tailed significance level was accepted as $p<0.05$ for all analyses. To eliminate the possibility of biased evaluation on CDT scoring in pre and post-treatment comparisons; intraclass correlation coefficient (ICC) analysis was used. The agreement level between the principal and blinded raters' scorings of CDT was assessed.

Associations between severity of OSA and cognitive test scores were examined with One-Way Analysis of Variance on ranks (Kruskal-Wallis H test). To study possible associations between sleep assessments and cognitive tests, we used correlation analysis and the results will be given in Spearman's rank correlation coefficients (r_s).

Results

Characteristics of the Overall Sample

Thirty-three patients diagnosed with OSA participated in the study (Figure 1). Data of one participant were removed because the low educational level caused missing value above 5% in cognitive tests. Although recommended, two of the patients refused to use CPAP device, thus their data were also not included to the analysis. Consequently, 30 patients with OSA included

to the baseline analysis, whose cognitive and psychological test results were compared with 30 healthy controls. Control group comprised of age and education matched volunteered participants who did not report sleep-breathing disorder. The minimum age for participation was set at 60. The age of the participants were 60 years and above for both groups.

Polysomnographic assessment results of $OSA_{baseline}$ patients (n=30; female 56.7%) are given in Table 1. Among these, 21 patients (70%) had diagnosis of hypertension and 5 (30%) had diabetes mellitus type II; 4 had no medical history. None of our patients had diagnosis of any type of dementia. Eleven patients (36.7%) had moderate and 19 patients (63.3%) had severe OSA. None of them were under insulin treatment or had no past cerebrovascular incident. All patients reported OSA related symptoms such as snoring (n=30, 100%), witnessed apnea (n=23, 76.7%), and daytime sleepiness (n=20, 66.7%). Mean ESS scores were in a range between 1-18 (median =5), and 24 of these patients had ESS ≤10.

Thirty patients who were recommended CPAP treatment and had informed consent were called for follow-up examinations after 6 months; 14 patients dropped out due to device adaptation problems and/or not showing up at control assessments. Sixteen of the patients with OSA attended the cognitive assessment after treatment and comprised our follow-up group. The follow-up comparisons were run with 16 patients (8 women, 8 men) that will be mentioned as $OSA_{follow-up}$. Average duration of CPAP usage was 6.9±2.1 months (median =6; range =5-9 months).

Volunteered participants (n=30; 50%) with MMSE scores >24 (M =29.28; SD =0.75) comprised our cognitively normal comparison group which was recruited as CG. Mean ESS score of the CG was 1.0 (SD =1.15) within the range of 0-3 (median =1). Among CG, 10 (33.4%) had diagnosis of hypertension and 4 (13.4%) had diabetes mellitus type II; 16 (53.4%) had no medical history. None of them were under insulin treatment or had any past cerebrovascular incident.

Table 1. Polysomnographic measurement results of $OSA_{baseline}$ patients

	$OSA_{baseline}$ (n=30)
	n (%)
Severity	
Moderate	11 (36.7)
Severe	19 (63.3)
	Mean ± SD
Polysomnographic measurements	
Apnea-hypopnea index	38.89±16.53
Oxygen desaturation index	35.79±17.92
Minimum oxygen saturation (%)	77.27±8.41
Mean oxygen saturation (%)	93.24±1.82
SpO_2<90% (sc)	9.5±14.31

SD: Standard deviation, SpO_2: Pulse oxygen saturation

Baseline Comparisons of OSA Group and Control Group

Socio-demographic features of $OSA_{baseline}$ and CG revealed no significant differences in terms of age (p=0.104), education year (p=0.414), and gender (p=0.409). But, two subgroups had differed at ESS (p=0.001) and BMI (p=0.002) showing that CG had lower sleepiness scores and lower BMI than $OSA_{baseline}$ patient group (Table 2).

The comparisons between the patient group and the healthy controls showed that, $OSA_{baseline}$ patients performed almost the same level as CG on attention and psychomotor speed test (Table 3). However, CDT (p=0.040) and phonemic fluency (p=0.049) performances of patients with OSA were significantly worse as compared to CG. In the Logical Memory subtest of WMS-R, immediate recall performances also showed difference at the lower significance (p=0.048). The difference of two groups' stroop test performance remained at significancy limit (p=0.050).

At the baseline evaluation, assessment of memory revealed significant differences both at CVLT learning (p=0.018) and delayed free recall (p=0.024) scores between $OSA_{baseline}$ and control group. Learning and delayed recall performances of $OSA_{baseline}$ were lower than CG (Table 3).

$OSA_{baseline}$ group showed no significant difference on digit span (both forward and backwards), TMT (both A and B), semantic

Table 2. Demographic variables and clinical screening results of study sample

	$OSA_{baseline}$ (n=30) (17 female; 56.7%)		CG (n=30) (15 female; 50%)		
	Median	**IQR (25-75%)**	**Median**	**IQR (25-75%)**	**p**
Age, years	64	6 (62-68)	66	8 (61-69)	0.104
Education, years	5	5.25 (5-10.25)	9.5	6 (5-11)	0.414
ESS	5	6.5 (2-8.5)	1	2 (0-2)	0.001*
BMI	32	7.5 (30-37)	27.3	4.5 (25.4-28.3)	0.002*
GDS	3	6 (1-7)	5	5.5 (3.3-9)	0.202

*Significant difference, p<0.05, OSA: Obstructive sleep apnea, CG: Control group, IQR: Interquartile range, ESS: Epworth sleepiness scale, BMI: Body mass index, GDS: Geriatric depression scale

fluency, stroop test, logical memory delayed recall, and CVLT immediate free recall and recognition scores as compared to CG.

Associations Between OSA Severity on Cognition

Analysis of variance showed that the OSA severity had significant effect [$\chi^2(1) = 5.292$, p=0.021] on CVLT delayed recall. Patients with moderate OSA had higher delayed recall scores (mean rank =11.90) than patients with severe OSA (mean rank =6.95), in which the higher scores indicating better performance.

Relation Between Sleep Measurements and Cognitive Tests

Correlation analysis was run between sleep measurements (ESS, AHI, ODI) and all neuropsychological test scores of $OSA_{baseline}$ patient group. Correlations were controlled for BMI, as covariant. As a result, CDT baseline scores showed significant correlation with AHI (n=28, r_s=-0.528, p=0.004) and ODI (n=28, r_s=-0.500, p=0.007). However, the correlation between ESS and baseline CVLT learning scores (n=29, r_s=0.347, p=0.047) lost its significance after controlling for BMI (n=29, r_s=0.201, p=0.746).

Cognitive Changes After CPAP Treatment

The effect of CPAP treatment was analyzed with repeated measures tests. Analysis results showed that CDT performances of older patients with OSA improved significantly after the CPAP treatment (p=0.046). The inter-rater reliability at the baseline evaluation revealed that 85.6% of the variance was real [ICC (2, 1) =0.856; p<0.001]. For the post-treatment, ICC was 0.636 (p=0.040). The significant difference between CDT scores of $OSA_{baseline}$ and $OSA_{follow-up}$ maintained even calculated with the scorings of the other rater (p=0.008).

Another significant difference was found in CVLT immediate recall (p=0.044), learning (p=0.017), recognition (p=0.033), and also false positive recognition (p=0.046) scores between baseline and post-treatment assessments. While significant difference indicates an improvement in CVLT immediate recall and learning scores; CVLT false positive recognition score

Table 3. Comparison of neuropsychological test scores between $OSA_{baseline}$ and CG before CPAP treatment

	CG (n=30)		$OSA_{baseline}$ (n=30)				
	Median	IQR (25-75%)	Median	IQR (25-75%)	U	p	r
Attention							
Digit Span Forward	5	0.75 (5-5.75)	5	1 (4-5)	173.0	0.068	0.236
Psychomotor Speed							
TMT-A	50	51 (32-83)	70.5	26.75 (59.75-86.5)	116.0	0.070	0.238
Executive Functions							
Digit Span Backward	4	0.75 (3.25-4)	3.5	1 (3-4)	174.0	0.086	0.210
Semantic fluency	18	5.5 (15.25-20.75)	17	9.25 (14-20.75)	178.0	0.260	0.145
Phonemic fluency	27.5	16.5 (23-40.5)	22.5	26.75 (59.75-86.5)	132.0	0.049*	0.173
TMT-B	154	113 (110-223)	188	136.25 (157-293.25)	122.5	0.097	0.214
Stroop Test Time difference False response	 41 1	 34 (35.5-69.5) 2 (0-2)	 61.5 1	 38.25 (45.75-84) 3 (0-3)	 103.5 193.5	 0.050 0.805	 0.252 0.032
Clock Drawing Test	5	0 (5-5)	5	1 (4-5)	160.0	0.040*	0.265
WMS-R Logical Memory Immediate recall (Z-scores)	58.4	18.75 (45.85-64.6)	45.8	12.48 (39.6-52.08)	137.5	0.048*	0.255
WMS-R Logical Memory Delayed recall (Z-scores)	56.3	16.7 (41.7-58.4)	45.8	8.3 (41.7-50.0)	120.5	0.069	0.237
Memory (CVLT)							
Immediate free recall	6	2 (6-8)	6	3 (5-8)	183.0	0.490	0.089
Learning score	54	10 (49-59)	45.5	15 (40-55)	116.5	0.018*	0.304
Perseveration	1	4 (1-5)	6	6 (2-8)	146.0	0.138	0.191
Delayed free recall	12	3 (11-14)	10	4 (8-12)	121.5	0.024*	0.290
Recognition False positive	16 1	1 (15-16) 2 (0-2)	15 1	1 (15-16) 2 (0-2)	175.5 155.5	0.351 0.716	0.120 0.049

*Significant difference between control group and $OSA_{baseline}$ patient group, p<0.05, IQR: Interquartile range, U: Mann-Whitney U test, r: Effect size, TMT-A: Trail making test form A, TMT-B: Trail making test form B, WMS-R: Wechsler memory scale-revised, CVLT: California verbal learning test

Table 4. Neuropsychological test scores of patients with OSA after CPAP treatment

	$OSA_{baseline}$ (n=16)		$OSA_{follow-up}$ (n=16)				
	Median	IQR (25-75%)	Median	IQR (25-75%)	Z	p	r
Attention							
Digit Span Forward	5	0 (5-5)	5	1 (4-5)	-1.414	0.157	0.250
Psychomotor Speed							
TMT-A	78.5	65.5 (48-104)	66	33 (53.5-83.5)	-1.521	0.128	0.266
Executive Functions							
Digit Span Backwards	3.5	1 (3-4)	3.5	1 (3-4)	-0.447	0.655	0.078
Semantic fluency	17	8 (13.5-20.5)	17	10 (13-22.5)	-0.912	0.362	0.161
Phonemic fluency	22	13 (19-29)	21	19 (18-34)	-0.492	0.622	0.087
TMT-B	201	96.5 (176.5-290)	172.5	121.75 (131-200)	-1.786	0.070	0.316
Stroop Test Interference time False response	 46 0	 31.5 (42-66) 2 (0-2)	 42 0	 49 (31-71) 0 (0-0)	 -1.201 -1.450	 0.230 0.147	 0.212 0.256
Clock Drawing Test	5	1 (4.5-5)	5	0 (5-5)	-2.000	0.046*	0.354
WMS-R Logical Memory Immediate recall (Z-scores)	41.7	14.75 (41.7-50)	45.4	10.40 (40.9-55.6)	-0.210	0.834	0.037
WMS-R Logical Memory Delayed recall (Z-scores)	45.8	18.18 (36.36-54.5)	50	12.47 (41.7-52.08)	-1.481	0.140	0.262
Memory (CVLT)							
Immediate free recall	7	4 (5-9)	8.5	3 (7-10)	-2.010	0.044*	0.177
Learning score	49	17 (42-58)	57	13.5 (47.5-60.5)	-2.387	0.017*	0.422
Perseveration	6	6 (2.5-8)	7.5	4 (5-9)	-1.134	0.257	0.201
Delayed free recall	10	4 (8-12)	11	3 (9.5-12)	-0.602	0.547	0.106
Recognition False positive	15 2	1 (15-16) 3 (0-3)	16 1	1 (15-16) 1 (1-1.5)	-2.126 -1.987	0.033* 0.046*	0.376 0.353

*Significant difference between $OSA_{baseline}$ and $OSA_{follow-up}$ patient group, p<0.05, IQR: Interquartile range, Z: Wilcoxon Signed-rank test, r: Effect size, TMT-A: Trail making test form A, TMT-B: Trail making test form B, WMS-R: Wechsler memory scale-revised, CVLT: California verbal learning test

was declined after CPAP treatment. However, no significant difference was observed at CVLT delayed recall scores after CPAP treatment (Table 4).

$OSA_{follow-up}$ group showed no significant difference on digit span (both forward and backwards), TMT (both A and B), semantic and phonemic fluency, Stroop Test, logical memory (both immediate and delayed recall), and CVLT delayed free recall scores as compared to $OSA_{baseline}$.

Discussion

In this study we aimed to contribute to the accumulating knowledge about the neurocognitive deficits in patients with OSA and the probable benefit of CPAP treatment with a prospective aspect. The prominent result of our study showed the positive effect of CPAP on memory functions in patients with OSA older than 60 years of age after 6-months of treatment.

At the baseline evaluation, OSA patients performed similarly with the controls on attentional test and psychomotor speed test. Yet, they performed significantly worse in clock drawing and phonemic fluency. The difference between CG and OSAS patient's Stroop Test performance was at the level of statistical significance. With regard to memory, there were significant differences both at CVLT learning and delayed free recall performances, and immediate recall of the logical memory subtest of WMS-R on the favor of worse performance in the patient group. Moreover, OSA severity was positively related with the decline in CVLT delayed recall.

In the follow-up, we observed that clock drawing performance, CVLT immediate recall, learning, recognition, and false positive recognition scores of the OSAS patients were improved significantly.

Considering previous studies on cognition in older OSA patients, we are presenting almost similar results in the patients with OSA over 60 years of age and additionally presenting the examination of memory through its phases. Most of the sleep-memory studies were designed under experimental conditions to apply memory tasks before and after sleep in a laboratory environment (33). However, learning and retrieval phases of

memory tests may be very informative at the clinical setting whether OSA has an impact on cognitive functioning of aging patients.

Memory has three information processing phases; i.e., encoding, consolidation and retrieval. In the verbal memory tests, total learning scores are being calculated from the sum of free recalled items of word list's each learning trial; which can be referred to encoding phase. We evaluated verbal memory with a word list (CVLT) and a story that has emotional and spatiotemporal context (WMS-R logical memory subtest) in this study. In the memory tests of moderate to severe OSA patients over 60 years of age, we observed a decrease in learning scores and delayed free recall scores compared to the matched control group. After 6 months of regular CPAP treatment, the disruptive effect of OSA on learning eliminated at the follow-up examination: As the immediate recall increased and learning ability improved then the need of recognition cues was observed to decline. Thus, the increase at the learning score in favor of the post-treatment examination indicates an improvement in the encoding phase of the memory. These findings of ours are in line with the studies reporting that OSA impairs memory (5,34) and those memory functions benefit from CPAP treatment (18,35). Retrieval phase, recalling of memory, refers to accessing the information which have already been encoded, and can be assessed with the "delayed recall" performance in memory tests. Consistently with the number of previous studies reporting that patients with OSA experience difficulties in memory phases such as free recall (36) while recognition was intact (7,8). Also, retrieval phase is the phase of the memory on which we observed the severity effect: Severe OSA group had worse delayed recall scores than moderate OSA group before treatment. In addition to the difficulties in learning and recalling the word list, the immediate recall of the logical memory task was also found to be affected in older OSA patients as compared to CG. Nonetheless, in the immediate recall of WMS-R logical memory subtest, which is primarily a working memory task, we did not observe the expected significant positive effect of treatment, even though an improvement was apparent.

Among the executive functions i.e., working memory, phonemic fluency, cognitive flexibility, set shifting and planning are other cognitive domains that have been repeatedly reported to be impaired in adults with OSA (37). Our results revealed that response inhibition which requires cognitive flexibility and set shifting, is impaired in older patients with OSA in comparison to CG. However, the difference was manifested at the significance level. This result may be limited by the small sample size. Another prominent finding of our study revealed that patients with OSA perform worse on planning and visuoconstruction task in comparison to CG which is consistent with the studies listed in the review presented by Saunamäki and Jehkonen (37). The decline in planning and praxis ability of the patients with OSA aged over 60 years significantly benefited from 6-months of CPAP treatment. CDT, measures visual and spatial skills with symbolic representations that evaluate executive and praxis functions (38). Since the instruction of the CDT contains two-stepped instruction, it is also an executive operation that requires holding the information online for goal-directed behavior. CDT showed negative correlation with sleep measurements (AHI and ODI) of $OSA_{baseline}$ group, leading us to accept this test as a representative assessment of executive function affected by desaturation. We believe, this simply administered but informative test should be included in the cognitive evaluations of patients with OSA.

The task of finding words with a phonemic cue requires scanning widespread the association cortices, whereas semantic fluency task is limited to the temporal brain areas (39). In studies evaluating cognition in patients with OSA, phonemic fluency was reported to be negatively affected by this sleep breathing disorder (40). Here we also observed a decline in phonemic fluency in older patients with OSA. However, patient and control groups performed close to each other on the semantic fluency task. Thus, we can formulate that the attentional system is relatively more affected, while OSA has no obvious effect on semantic storage. Probably devalued by the small sample size, the improvement we observed at phonemic fluency after CPAP treatment couldn't reached the significance level.

In terms of the other cognitive tests, our research results were in line with CPAP treatment efficiency studies of TMT-A (17,18) and digit span (36) that did not reveal any significant change. However, TMT-B has been repeatedly reported to be affected from OSA (12,41) and improved after CPAP treatment (41). Although we expected an improvement in set shifting ability within sustained attention, our results revealed no significant difference.

Study Limitations

This study has some limitations and strengths. Small sample size was one of the limitations. On the other hand, as the number of participants increase it becomes difficult to control confounding factors that may affect cognitive functions in the older individuals. Another limitation was the missing data of untreated older patients with OSA. The comparison of cognitive test results of CPAP treated patients with OSA and who refused to use CPAP treatment were considered to be valuable. However, the number of OSA patients who did not agree to use CPAP therapy could not reach the level for statistical analysis, within the planned duration of the study. For this very valuable piece of information our further motivation is to add a CPAP-free control group. Examining the memory functions to its processes enabled us to conclude that the OSA may impair learning and

free recalling of the recently encoded memory inputs, which cannot be achieved with screening tests. The significant difference between CDT scores of $OSA_{baseline}$ and $OSA_{follow-up}$ maintained even calculated with the scorings of the other rater (Interrater reliability was met both at the baseline and follow-up evaluations of clock drawing).

Conclusion

We reported the data on the cognitive functionality in OSA patients over 60 years of age by comparing with matched CG, and cognitive change in the treated group. The absence of psychiatric or malign medical conditions presented relatively pure results about cognitive functions. A number of executive functions and memory functions were found to be affected in our sample. Detailed assessment of cognitive abilities showed that learning and free recall phases of memory were disrupted while recognition was intact. The cognitive impairment that may be related to OSA found to be benefited from a sufficient period of treatment, i.e., average of 6 months of effective CPAP use, even in individuals over 60 years of age. There are few studies revealing the effect of OSA on memory processing phases, while this provides very important information for discriminative diagnosis among neurodegenerative disorders. Thus, we believe that the study required to be replicated with a larger number of participants. For the further researches we are motivated to combine the results with structural and functional neuroimaging at resting state is believed to be more informative.

Acknowledgements: The authors give special thanks to participants, technical staff in sleep laboratory in Istanbul University Pulmonary Diseases Department, Geropsychiatrist Prof. Sibel Cakir, Geriatic Internal Medicine specialist Raim Iliaz, MD, and Behavioral Neurologist Prof. Hakan Gurvit.

Ethics

Ethics Committee Approval: All procedures performed in this study involving human participants were in accordance with the ethical standards of İstanbul University, İstanbul Faculty of Medicine Ethics Committee for Clinical Research and with the Helsinki declaration (no: 2023-1782132).

Informed Consent: All participants provided written informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.K., Z.B., Concept: G.B., M.A.K., A.T.Ç., Design: G.B., Data Collection or Processing: E.K., Z.B., D.B., Analysis or Interpretation: Z.B., D.B., Literature Search: A.T.Ç., D.B., Writing: G.B., Z.B., D.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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