EREDETI KÖZLEMÉNY

ORIGINAL ARTICLE

The effect of disease severity and chronic CPAP-therapy on cognitive functions and event related potentials in OSAS

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Background and purpose – Obstructive sleep apnea syndrome (OSAS) may cause daytime sleepiness, mood changes and dysfunction in various cognitive areas due to recurrent arousals and / or chronic intermittent hypoxia. Different possibilities have been proposed regarding the most affected cognitive areas and mechanisms of OSAS. However, it is difficult to compare findings of the different studies due to the fact that individuals with different disease severities were included in the study groups. In the current study, we aimed to determine the relationship between severity of OSAS and cognitive functions, to investigate the effect of continuous positive airway pressure (CPAP) titration treatment on cognitive functions and the relationship between these changes and electrophysiological potential.
Methods – The study included 4 groups of patients with simple snoring and mild, moderate and severe OSAS. In the pre-treatment evaluations, verbal fluency, visuospatial memory, attention, executive functions, language abilities and electrophysiological tests for event-related potential were performed.

A betegségsúlyosság és a krónikus CPAP-terápia hatása a kognitív funkciókra és az eseményhez kapcsolódó potenciálokra OSAS-ban
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Háttér és cél – Az obstruktív alvási apnoe szindróma (OSAS) az ismétlődő ébredések és/vagy a krónikus intermittáló hypoxia miatt nappali álmosságot, hangulatváltozásokat és különböző kognitív területek működési zavarát okozhatja. Az OSAS által leginkább érintett kognitív területekre és annak mechanizmusára vonatkozóan különböző lehetőségeket javasoltak. A különböző vizsgálatok eredményeit azonban nehéz összehasonlítani, mivel a vizsgálati csoportokba különböző súlyosságú betegséggel küzdő egyéneket vontak be. Jelen tanulmányban az volt a célunk, hogy meghatározzuk az OSAS súlyossága és a kognitív funkciók közötti összefüggést, megvizsgáljuk a folyamatos pozitív légúti nyomás (CPAP) titráló kezelés hatását a kognitív funkciókra, valamint e változások és az elektrofiziológiai potenciál közötti kapcsolatot.
Módszerek – A vizsgálatban négy csoportban egyszerű horkoló, valamint enyhe, közepes és súlyos OSAS-ban szenvedő betegek vettek részt. A kezelés előtti értékelések során verbális folyékonyságot, vizuospatialis memóriát, figyelmet, végrehajtó funkciókat, nyelvi képességeket teszteltek, és az ese-

The same procedure was reapplied after 4 months of CPAP-therapy.
Results – Long-term recall scores and total word fluency scores were found to be low in the groups with moderate and severe disease compared to the patients with simple snoring (p: 0.04, p: 0.03, respectively). The information processing time was higher in patients with severe disease compared to patients with simple snoring (p: 0.02). The P200 and N100 latencies related to event related potentials (ERP) were significantly different between the groups (p: 0.004, p: 0.008, respectively). After CPAP treatment, significant differences were found in N100 amplitude and latencies and all cognitive areas except abstraction. In addition, N100 amplitude and latency change rate as well as change in attention and memory abilities were correlated (r: 0.72, p: 0.02; r: 0.57, p: 0.03, respectively).
Conclusion – In the current research, disease severity was found to negatively affect long-term logical memory, sustained attention and verbal fluency. Moreover, significant improvement was detected in all cognitive areas with CPAP treatment. The findings of our study support that changes in N100 potential have the potential to be used as a biomarker that can be used to monitor cognitive function recovery after treatment.

Keywords: event related potentials, sustained attention, verbal memory, abstraction, verbal fluency

ményhez kötött potenciál elektrofiziológiai vizsgálatait végezték el. Ugyanezeket az eljárásokat négy hónapnyi CPAP-terápia után újra elvégezték.
Eredmények – A hosszú távú emlékezet pontszámai és a teljes szófolyamatossági pontszámok alacsonyak voltak a közepesen súlyos és súlyos betegségben szenvedők csoportjaiban az egyszerű horkolásban szenvedő betegekhez képest (p: 0,04, illetve p: 0,03). Az információfeldolgozási idő hosszabb volt a súlyos betegségben szenvedő betegeknél az egyszerű horkolásban szenvedő betegekhez képest (p: 0,02). Az eseményhez kapcsolódó potenciálokhoz (ERP) kapcsolódó P200 és N100 latenciák szignifikánsan különböztek a csoportok között (p: 0,004, illetve p: 0,008). A CPAP-kezelést követően szignifikáns különbségeket találtunk az N100 amplitúdóban és latenciában, valamint az absztrakció kivételével minden kognitív területen. Ezenkívül az N100 amplitúdó és latencia változásának aránya, valamint a figyelem- és a memóriaképességek változása korrelált egymással (r: 0,72, p: 0,02; r: 0,57, p: 0,03).
Következtetés – A jelen kutatásban a betegség súlyossága negatívan befolyásolta a hosszú távú logikai memóriát, a fenntartott figyelmet és a verbális folyékonyságot. Ezen túlmenően a CPAP-kezeléssel szignifikáns javulást észleltek valamennyi kognitív területen. Vizsgálatunk eredményei alátámasztják, hogy az N100 potenciál változásai olyan biomarkerként használhatók, amely a kezelés után a kognitív funkciók helyreállításának nyomon követésére használható.

Kulcsszavak: eseményhez kapcsolódó potenciálok, fenntartott figyelem, verbális memória, absztrakció, verbális folyékonyság

Obstructive sleep apnea syndrome (OSAS) is a syndrome characterized by chronic intermittent hypoxia during sleep with episodic and recurrent collapse of the upper airway. obstructive sleep apnea (OSA) can lead to daytime sleepiness, mood changes, and dysfunction in various cognitive domains due to recurrent arousals and/or chronic intermittent hypoxia[1]. Different possibilities have been proposed regarding the most affected cognitive areas and mechanisms of OSAS. Although most studies have found sustained attention, long-term memory, visuospatial, motor abilities, and executive functions to be impaired by OSAS, there is consensus that language functions are preserved[2–5]. However, it is difficult to compare findings of the different studies due to the fact that individuals with different disease severities were included in the study groups, the definition of severity varied between studies, and the patients were investigated in different sampling groups[6–7].

Event-related endogenous potential (ERP) shows the electrical activity that occurs in response to an external event or stimulus during information processing in the brain. ERP provides information about the neural basis of

cognitive functions such as selective attention, recognition memory, decision-making, and language functions[8], and has the potential to be more sensitive biomarker of cognitive improvement in OSA[9]. Studies examining changes in ERP in OSAS patients have reported conflicting results. Using P300 data, some studies have suggested that ERP potential amplitudes decrease and latencies are prolonged in OSAS patients[9–13]. However, some studies show no difference in ERP potentials in OSAS patients[14]. Published data on early components of ERP (N100, P200, N200) in patients with mild to moderate OSAS are limited.

Studies have shown that titration therapy with continuous positive airway pressure (CPAP) provides a specific clinical improvement in OSAS patients, relieving sleepiness and improving cognitive function[15–20]. Some have shown limited or no improvement in execution and attentional functions after CPAP treatment[21, 22]. However, most of these studies have been conducted either with severe OSAS patients or in very heterogeneous groups of patients or with different durations of CPAP use. The study of cognitive improvement after CPAP titration therapy is, therefore, necessary to obtain reliable data on persistent cognitive dysfunction due to OSAS.

Recent studies indicate that cognitive deficits may also exist in patients with simple snoring[23]. On this base, OSAS patients have been classified according to the severity of disease using the apnea-hypopnea index (AHI), which classifies patients according to the degree of sleep interruption and chronic intermittent hypoxia. In the current study, we aimed to; 1. compare the differences in cognitive performance and ERPs between 4 groups of OSAS patients with different severity of disease at baseline, 2. determine whether cognitive performance and ERPs may change under CPAP treatment, and 3. determine the association between changes in ERPs and cognitive performance after 4 months of continuous CPAP treatment.

Materials and methods

Sample

This prospective observational study was approved by the Clinical Research Ethics Committee of Erenköy Psychiatric and Neurological Diseases Training and Research Hospital (03.10.2016 / Decision No: 6). The study was conducted between September 2016 and October 2017 with patients admitted to the sleep laboratory of Erenköy Psychiatric and Neurological Diseases Training and Research Hospital with all-night polysomnography (PSG) diagnosed with OSAS or simple snoring. Patients aged 18-50 years with at least primary education were included in the study. All participants provided written informed consent. Patients with a history of unilateral or bilateral conduction type, sensorineural or mixed hearing loss and color blindness, diagnosed ischemic heart disease and/or heart failure, diseases that may cause cognitive deficits (mental retardation, neurodegenerative diseases, metabolic disorders, history of drug, substance, and alcohol use), chronic respiratory diseases (asthma, COPD), sleep disorders other than OSAS (hypersomnia, periodic leg movement syndrome, insomnia, inadequate sleep activity), known neurological disorders (ischemic/hemorrhagic cerebrovascular disease, epilepsy, head trauma with loss of consciousness for more than 6 hours), known psychiatric disorders (mood disorders, psychosis, anxiety disorders), Beck Depression Inventory score of 16 and more, use of psychostimulant or hypnotics, and subjects with a standardized Mini-Mental Test score of 24 or less were excluded from the study.

Application

All participants underwent a standardized PSG procedure. Patients slept all night in a sleep center. Standard surface electrodes were used to record electroencephalographic (six-channel EEG leads: C4-A1, C3-A2, O1-A2, O2-A1, F4-A1, and F3-A2), two-channel electrooculographic, electromyographic (submental, right, and left anterior tibialis muscles), and electrocardiographic data. Nasal–oral thermocouples were used to monitor airflow while body position and thoracic and abdominal movements served as indicators of respiratory effort. Blood oxygen saturation was monitored with pulse oximetry with the sensor placed on the earlobe. Sleep latency, sleep efficiency, percentage of sleep time in each sleep stage, leg movements, and other polysomnographic parameters were calculated using a Neurosoft analysis program.

Patients diagnosed with OSAS were divided into three groups of mild (5-15 / hour), moderate (15-30 / hour), or severe (30 + / hour) OSAS based on the Apnea-Hypopnea Index (AHI). Patients with simple snoring were included in the control group. The sample size consisted of a total of 80 patients with OSAS, with at least 20 patients in each group. Patients with moderate to severe OSAS who were offered CPAP treatment were invited for re-evaluation after four months. Patients were adviced to use CPAP treatment for at least 5 days/week and at least 5 hours/day. Only those patients who reported a decrease in their symptoms and complied with the use of the device as prescribed were included in the study. Data from CPAP devices with recording capability were examined using the output of the device to determine the regularity of use of CPAP treatment. Patients with CPAP devices that did not have a recording function were verbally interviewed about the decrease in their symptoms and duration of use. A total of 17 patients (mild OSAS: 8, severe OSAS: 9) who could use the CPAP device as indicated were evaluated after CPAP therapy. For re-evaluation

ERP, electrophysiological examinations and neuropsychiatric tests were performed on all patients after CPAP treatment.

Assessment of cognitive functions

Cognitive assessment tests were administered to patients in the morning in a quiet room and after confirmation that they were not hungry and had slept 7 hours with assessments lasting approximately 40-50 minutes. The evaluations were performed by the same physician (TE) who had undergone theoretical and practical training on how to perform the tests before the start of the study. Short breaks were taken during the neurocognitive tests according to need, test duration, and test diffuculty. The cognitive tests were performed after polysomnography before regular CPAP use.

Memory tests

Weschler Memory Scale – Logical Memory Sub-Test: This is a subtest of Wechsler Memory Scale and consists of two stories, each one paragraph long. The scoring is based on the items contained in the stories. The Turkish application of these stories was done by Öget Öktem at the Neuropsychology Laboratory of Istanbul Faculty of Medicine.

Weschler Memory Scale – Visual Production Test: The visual production test, a subtest of Wechsler Memory Scale, tests short and long-term memory. Figures are presented on labeled cards A, B, and C respectively. Self-recall and recognition scores are evaluated separately.

Attention and working memory tests

Number Range Test: The Number Range Test, a subtest of the WAIS – R battery, is the most commonly used attention / short-term memory test. Scores for the forward and backward number range are scored separately and as the sum of the two.

Visual-spatial function test

Benton Facial Recognition Test: The Benton Facial Recognition Test is used to visually and perceptually assess visuospatial functions to examine the inferior temporal regions of the posterior association cortex (i.e., perception of the stationary properties of the shape from below).

Executive functions

Verbal Fluency Test: The controlled word association test, also known as verbal fluency test, is tested by counting words from a given letter in one minute. The letters K, A, S are used for verbal fluency test, and counting animals is preferred as semantic fluency test.

Stroop Test: Standardized application and registration forms were developed for the Turkish form of the test as part of the standardization of the BILNOT battery. The Stroop test is a very sensitive test that examines interference resistance and the tendency to suppress response. The Stroop test assesses selective attention, response inhibition, concentration, and information processing.

Abstract Thinking: This test is a sub-test of the WAIS-R used to evaluate abstract thinking ability. It asks about the similarity between two objects with concrete and abstract similarities. Concrete similarities refer to the properties of the objects (e.g., apple–banana: both have skin) that can be seen or touched. Abstract similarities refer to more universal properties or to a common classification (e.g. apple–banana: both are fruits).

Language functions

Boston Naming Test (BAT): BAT primarily measures the ability to recognize and name objects. This test is also thought to reflect the ability to process semantic information. BAT score consists of the sum of words correctly recalled without a clue, with a semantic clue, and with a phonemic clue.

The Beck depression scale and standardized mini-mental test were also used with the patients.

Acquisition and analyses of electrophysiological records

Electrophysiological examinations of all participants were performed early in the morning in a room isolated from light and electrical activity. EEG monitoring was performed using a NeuronSpectrum 5/P 19-channel digital EEG device (Neurosoft Inc, Ivanova, Russia). The room temperature was kept at 23˚C to avoid excessive sweating. During the recordings, subjects sat on a comfortable chair, and their vigilance level was kept as constant as possible by verbal commands. 19-channel computerized EEG recordings were acquired via Ag-AgCl plated disk electrodes placed at 19 points on the scalp according to the international 10-20 nomenclature, and recorded the maximum resting state of the subjects. Active electrodes were placed on the frontal (FP1, FP2, F3, F4, F7, F8, FZ), central (C3, C4, CZ), parietal (P3, P4, PZ), temporal (T3, T4, T5, T6), and occipital (O1, O2) areas. An average of A1 and A2 was taken as the reference electrode. Care was taken to ensure that all electrode impedances were below 5 kΩ. The sampling rate was set to 512 Hz, with 0.05 Hz as the high-frequency filter and 70 Hz as the low-frequency filter.

ERP was recorded using the auditory odd-ball two-tone discrimination method. Two different horns were given to both ears simultaneously, 50 msec, 80dB, 1-second frequency. Patients were asked to discriminate target

Table 1. *Demographic characteristics and comparison of simple snoring and OSAS patients groups*

	Simple snoring (n: 26, m: 13, f: 13)	Mild OSAS (n: 24, m: 21, f: 3)	Moderate OSAS (n: 25, m: 21, f: 4)	Severe OSAS (n: 29, m: 28, f: 1)	Total (n: 104, m: 83, f: 21)	F/df	p
Age (mean±sd)	39.54±7.84	37.29±7.25	38.36±7.46	39.10±7.38	38.62±7.43	0.432	0.73*
Education level (year) (mean±sd, median)	12.04±4.03 (13.00)	12.54±3.21 (12.50)	11.80±3.52 (11.00)	11.52±3.75 (11.00)	11.95±3.62 (11.50)	3	0.841**
AHI (mean±sd)	2.62±1.14	8.99±2.79	21.34±5.06	58.93±24.28	24.29±26.10	101.58	<0.001*

AHI: apnea/ hypopnea index, OSAS: obstructive sleep apnea syndrome
*One way Anova test was performed.
**Kruskal-Wallis test was performed.

sounds (2000 Hz at 20% of frequency) from non-target sounds (80% at 1000 Hz frequency) using button presses in the hand. Rarely heard target sounds were noted as random. ERP recordings were performed in 3 blocks and 150 stimuli were given in each block. A block lasted for an average of 3 minutes, with breaks between blocks.

MATLAB based programs EEGLAB (version 13) and ERPLAB (version 5) were used to analyze the ERP signals. Data were re-filtered using 0.5 Hz as the low-frequency filter and 35 Hz as the high-frequency filter. A cleaning process was performed using the +/-70 microvolt base voltage method to determine and delete epochs that contained eye, muscle, and motion artifacts. Later, the recordings were rescanned for artifacts, and then, the filtered traces were segmented into 200 ms before stimuli and 800 ms after stimuli. Only the segments that were pressed at the correct time interval were included in the analysis. In this study, the P300 potentials obtained from Fz, Pz, and Cz electrodes, and the N100, P200, and N200 obtained from Fz were used.

Statistical analysis of data

Statistical Package for Social Sciences (SPSS) 24 was used for the statistical analysis of the results. Descriptive statistical methods (frequency, percentage, mean, standard deviation) were used to analyze the data. The variables were examined for normal distribution using visual and analytical.

Kruskal Wallis test and one-way ANOVA test were used to compare numerical data such as electrophysiological and cognitive data between groups with simple snoring, mild, moderate, and severe OSAS. For one-way Anova test, homogeneity was checked with Levene statistic test and Tukey test was applied if it showed homogeneous distribution according to homogeneity status. In the pairwise comparison of the data with significant differences in the Kruskal Wallis test, Bonferroni correction was applied and p value was taken as 0.008. For comparisons of CPAP titration data and electrophysiological data collected at baseline and 4 months later, the paired Student t-test was used for data with normal distribution, and Wilcoxon test for data with nonnormal distribution. The relationship between cognitive functions and electrophysiological data was analyzed using Pearson correlation test for data with normal distribution and Spearman correlation test for data with non-normal distribution. Results were analyzed with 95% confidence interval, $p<0.05$ significance level, and $p<0.01$ advanced significance level.

Results

Sociodemographic data

The sociodemographic data of the patients included in the study and the comparisons between the groups are shown in **Table 1**.

Assessment of cognitive functions in patients with simple snoring and OSAS

It was found that cognitive functions were similar in patients with simple snoring and OSAS, except for long-term logical memory, flexible thinking and verbal fluency. However, these differences were observed between patients with simple snoring and OSAS; no statistically significant differences were found between the mild/moderate/severe OSAS groups. Comparisons of the cognitive functions of patients divided into 4 independent groups according to the AHI scores are shown in **Table 2**.

Evaluation of event-related potential in patients with simple snoring and apnea

N100 amplitude was significantly different between the group with severe OSAS and the group with simple snoring. No statistically significant difference was found in the amplitudes of the P300, N200, and P200 components of the ERP between the four groups of patients. When

Table 2. *Comparison of cognitive functions according to simple snoring and OSAS severity (mean ± sd)*

Tests	Test outcome	Simple snoring (n: 26, m: 13, f: 13)	Mild OSAS (n: 24, m: 21, f: 3)	Moderate OSAS (n: 25, m: 21, f: 4)	Severe OSAS (n: 29, m: 28, f: 1)	F/df	p
Digit Span Test	Forward Digit Span (med)	5.54±1.79 (5.50)	5.83±1.12 (6.00)	6.16±1.24 (6.00)	5.79±1.08 (6.00)	3	0.54
	Backward Digit Span (med)	4.65±1.52 (5.00)	4.75±1.29 (5.00)	4.84±1.49 (4.00)	4.34±1.37 (4.00)	3	0.71
Weschler Memory Scale-Logical Memory	Short term memory	15.31±4.13	15.46±4.66	14.96±4.62	16.14±3.55	0.373	0.77
	Long term memory	15.12±3.11	14.41±3.98	*12.25±4.30**	*12.79±4.34**	2.833	*0.04*
Wechsler Memory Scale - Visual Reproduction Test	Short term memory (med)	10.31±3.79 (12.00) 1010.31±3.79 (12.00)	12.25±1.91 (13.00)	10.72±2.97 (12.00)	10.93±3.40 (12.00)	3	0.12
	Long term memory (med)	10.12±2.99 (10.00)	12.05±2.14 (13.00)	10.35±3.65 (12.00)	9.93±3.76 (11.00)	3	0.06
Stroop Test	Total Latency (med)	73.95±14.06 (71.9)	76.79±14.28 (76.52)	74.84±16.96 (70.70)	*87.31±19.83 (82.57)**	3	*0.02*
	Perseverative Errors (med)	1.32±1.86 (1.00)	*0.69±1.14 (0.00)*	1.68±3.48 (1.00)	1.96±2.52 (1.00)	3	0.33
Verbal Fluency Test	Animal Counting	23.69±8.24	20.00±4.89	22.12±3.74	19.45±7.11	2.52	0.06
	K-A-S Fluency	47.88±18.99	*35.88±13.52**	40.56±13.89	39.33±11.65	2.96	*0.03*
Benton Facial Recognition Test	Facial Recognition (med)	47.58±3.85 (49.0)	47.33±3.0 (49.0)	47.24±3.27 (47.0)	44.76±8.70 (47.0)	3	0.43
Similarities	Similarities Scores (med)	9.12±2.12 (10.0)	9.62±0.64 (10.0)	9.56±0.71 (10.0)	9.55±0.91 (10.0)	3	0.94
Boston Naming Test	Correct Naming (med)	28.25±2.83 (29.0)	28.92±1.21 (29.0)	28.08±2.76 (29.0)	27.59±2.86 (28.0)	3	0.46
	Correct with Semantic Clue	0.29±0.69 (0.0)	0.08±0.40 (0.0)	0.08±0.40 (0.0)	0.28±0.64 (0.0)	3	0.24
	Correct with Phonemic Clue	0.58±0.77 (0.0)	0.71±0.85 (0.0)	0.60±1.08 (0.0)	1.0±1.10 (1.0)	3	0.30

One way Anova and Kruskal Wallis test were performed. For one-way Anova test, homogeneity was checked with Levene statistic test and LSD test was applied if it showed homogeneous distribution according to homogeneity status and Tamhane's T2 post-hoc tests were chosen if it did not show homogeneous distribution. In the pairwise comparison of the data with significant differences in Kruskal Wallis test, Bonferroni correction was applied and p value was taken as 0.008. * p<0.05 or p<0.008 (Compared with simple snoring group in the p airwise comparison)

the latencies of the associated potentials were compared using the Bonferroni-corrected Mann-Whitney U test, the P200 latencies were found to be statistically significantly shorter in patients with severe OSAS than in patients with simple snoring and those with mild OSAS (p: 0.004 and p: 0.005, respectively). Pairwise comparisons between groups showed that the N100 latencies of patients with moderate OSAS were significantly shorter than those of patients with simple snoring (p: 0.008). A comparison of the cognitive functions of the patients, who were divided into 4 independent groups according to the AHI scores is shown in **Table 3**.

Investigation of changes in cognitive functions and ERP after CPAP therapy

The cognitive characteristics and electrophysiological data of patients with moderate and severe OSAS were re-

Table 3. *Comparison of ERP potentials according to simple snoring and OSAS severity (mean ± sd)*

ERP Potentials	Simple snoring	Mild OSAS	Moderate OSAS	Severe OSAS	F/df	p
P300 amp in Fz(med)	2.92 ± 1.99 (2.25)	3.58±2.16 (2.72)	4.52±3.27 (4.33)	3.48±2.07 (3.43)	3	0.535
P300 amp in Cz	4.11±2.19	3.40±1.72	4.84±2.82	4.31±2.71	1.148	0.335
P300 amp in Pz	4.26±1.61	3.57±1.39	5.04±2.79	4.47±2.37	1.668	0.180
P300 latency in Fz	309±34	315±25	304±30	310±33	0.272	0.846
P300 latency in Cz(med)	313±30 (320)	302±78 (324)	304±30 (302)	312±35 (322)	3	0.904
P300 latency in Pz	308±36	311±29	305±31	311±39	0.151	0.929
N200 amp(med)	1.83±1.10 (1.46)	2.34±0.91 (2.24)	1.76±1.39 (1.76)	1.73±0.77 (1.69)	3	0.132
N200 latency(med)	226±36 (216)	210±41 (202)	212±47 (210)	205±27 (200)	3	0.254
P200 amp	2.27±0.94	2.83±1.04	2.68±1.38	2.57±1.19	0.895	0.448
P200 latency(med)	155±23 (148)	160±30 (152)	144±33 (142)	134±17(138)*, **	3	*0.008*
N100 amp	4.86±1.57	5.11±1.76	4.68±1.20	6.39±2.33*	4.333	*0.007*
N100 latency(med)	85±6 (87)	86±8 (86)	75±17 (78)*	75±14 (81)	3	*0.006*

* p<0.05 or p<0.008 (Compared with simple snoring group)
** p<0.05 or p<0.008 (Compared with mild OSAS group)
One way Anova and Kruskal Wallis test were performed. For one-way Anova test, homogeneity was checked with Levene statistic test and LSD test was applied if it showed homogeneous distribution according to homogeneity status and Tamhane's T2 post-hoc tests were chosen if it did not show homogeneous distribution. In the pairwise comparison of the data with significant differences in Kruskal Wallis test, Bonferroni correction was applied and p value was taken as 0.008.

evaluated after 4 months of CPAP treatment. CPAP treatment was initiated in 54 patients but 37 patients discontinued it due to lack of compliance. Therefore, follow-up was performed in 17 patients who used the CPAP device regularly and whose AHI scores were below 5 during CPAP use. A comparison of cognitive functions and electrophysiological potential before and after treatment is shown in **Table 4**.

Investigation of the relationship between cognitive functions and ERP values that changed after treatment

It was found that the percentage change in cognitive functions and ERP values after treatment with CPAP was significant in patients with moderate and severe OSAS. In addition, a statistically significant positive correlation was found between the percentage change in N100 amplitude and the change in inverse number range scores (r: 0.52, p: 0.48). Similarly, a statistically significant and robust positive correlation was found between the percentage change in N100 amplitude and the number of perseverance errors in the Stroop Test (r: 0.72, p: 0.02). Also, a moderate but statistically significant positive correlation was found between the percentage change in N100 latency and long-term recall scores in the logical memory test (r: 0.57, p: 0.03). No significant correlation was found between changes in other ERP components and changes in cognitive function.

Discussion

Effect of disease severity and CPAP treatment on cognitive functions

In the current study, cognitive domains such as long-term logical memory, flexible thinking, and verbal fluency were found to deteriorate with severity in patients with OSAS. Cognitive functions such as attention, visuospatial functions, language functions, and abstraction were not affected by disease severity. However, after regular CPAP titration treatment for 4 months, improvements were observed in almost all cognitive domains (attention, visual and logical memory, verbal fluency, executive functions, abstraction, and naming). This improvement may indi-

Table 4. *Investigation of cognitive functions and event-related potentials after CPAP treatment (n: 17): (mean ± sd)*

Tests	Test outcome	Before PAP titration	After PAP titration	Z/df	p
Digit Span Test	Forward Digit Span	6,18±1,01	6,59±1,32	-1,94	*0,05**
	Backward Digit Span	4,88±1,40	5,71±1,53	-2,26	*0,02**
Weschler Memory Scale-Logical Memory	Short term memory	15,47±3,98	18,35±2,09	16	*0,01*
	Long term memory	12,80±4,21	17,07±2,71	14	*0,001*
Wechsler Memory Scale - Visual Reproduction Test	Short term memory	11,29±2,08 1010,31±3,79 (12,00)	12,65±1,80	-3,21	*0,001**
	Long term memory	9,93±3,43	11,93±3,01	-3,13	*0,002**
Stroop Test	Total Latency	80,98±19,72	72,45±17,18	-2,76	*0,006**
	Perseverative Errors	2,05±2,68	0,52±1,00	-2,33	*0,02*
Verbal Fluency Test	Animal Counting	18,65±8,30	24,35±4,40	16	*0,03*
Benton Facial Recognition Test	Correct Facial Recognition	45,06±11,03	49,59±3,31	-2,24	*0,02**
Boston Naming Test	Correct Naming	28,24±2,48	29,06±2,27	-2,57	*0,03**
P300 in Fz	Amplitude	3.62±2.19	3.58±1.84	11	0.94
P300 in Fz	Latency	308±30	299±93	-1.60	0.11*
P300 in Cz	Amplitude	4.40±2.76	4.17±2.34	13	0.53
P300 in Cz	Latency	309±33	322±44	13	0.11
P300 in Pz	Amplitude	4.41±2.01	4.80±1.76	12	0.40
P300 in Pz	Latency	308±34	316±48	12	0.42
N200	Amplitude	1.44±0.84	2.01±1.31	10	0.09
N200	Latency	204±36	208±39	10	0.60
P200	Amplitude	2.93±1.10	2.99±1.39	13	0.88
P200	Latency	133,29±29,88	156,0±22,55	-2,48	*0,01**
N100	Amplitude	5,80±2,09	5,10±1,36	-1,94	*0,05**
N100	Latency	68,80±15,26	86,13±4,98	14	*<0,001*

*Wilcoxon test was performed to compare the data of the dependent groups. Paired-Student T test was performed for other data.

cate an improvement in functions specific to patients with OSAS. The current study did not include healthy subjects as a control group, but compared patients with OSAS to patients with simple snoring. For this reason, the cognitive functions that are likely to differ between healthy controls and OSAS patients may not be as different as in the simple snoring group. In fact, previous studies have found that children who snore had impairments in neurocognitive functions[6]. In other words, the results of the current study support the fact that many cognitive deficits in patients with OSAS occur in the early stages of the disease.

Studies examining cognitive function after CPAP titration treatment in OSAS patients have yielded conflicting results. A detailed analysis of the available data suggests that despite the different cognitive domains examined, no significant differences were found in the early stages of CPAP treatment[15]; rather, significant differences were found in the later stages of treatment[24].

The underlying mechanisms of the relationship between sleep and cognition are not yet fully understood. According to Beebe and Gozal, deoxygenation of blood during OSA can impair the recovery process during sleep

and cause cellular damage in the central nervous system[24]. Also, it has been shown that gray matter concentration in the limbic regions, cingulate gyrus, prefrontal areas, caudate nucleus, and cerebellum are decreased in men with severe OSA[25]. This finding has been confirmed by other studies and generalized and localized cortical thinning have been found in individuals with severe OSA[26].

Most studies have reported that CPAP therapy contributes to neurotropic changes, improvement in chronic intermittent hypoxia and sleep quality, reduction in oxidative stress, and reduction in endothelial damage. Thus, CPAP titration can lead to restoration of white matter, thalamus, hypothalamus, frontal structures, and brainstem, as well as improvement in cognitive tests[27].

Effect of disease severity and CPAP therapy on event-related potentials

We found a significant prolongation of P200 and N100 latencies, ERP parameters related to attention, in OSAS patients. The absence of a significant difference in P300 latency between groups could be related to the cognitive impairment present in patients with simple snoring (control group), as previously mentioned. After treatment with CPAP, P200 and N100 latencies and N100 amplitudes showed improvement, whereas no significant difference was found in P300 amplitude and latency between groups or in the before / after comparison.

Several studies investigating the presence of cognitive impairment in OSAS with endogenous potentials associated with an auditory event. *Peng* et al. performed auditory P300 tests in OSAS patients, a simple snoring group, and a control group and found no difference in P300 amplitudes in all groups; however, the P300 showed a prolonged latency in the OSAS group[28]. It is suggested that auditory P300 latency may be indicative of cognitive dysfunction in OSAS and that chronic intermittent hypoxia affects latency prolongation[28]. *Vakulin* et al. compared 9 severe OSAS patients with healthy controls and found no change in N100 latency but reported prolonged P200, N200, and P300 latencies and decreased amplitudes of P200 and P300[29]. CPAP titration therapy was used in the same patients for three months after which P200 and N200 latencies did not improve, whereas P300 latency became shorter[29]. In contrast to this study, *Sangal* et al. reported that a visual ERP test was used in 40 patients with OSAS, and when the patients were reassessed after 2-4 months of CPAP titration therapy, no positive effect of treatment on P300 was observed[30]. The lack of significant improvement in P300 amplitude or latency after treatment with CPAP may be due to the need for longer treatment duration, although cognitive impairment may begin to improve earlier[30]. However, it has been reported that P300 impairment due to chronic intermittent hypoxia may be irreversible, or that visual pathways are more susceptible to hypoxic damage[30].

Conflicting data have also been reported on changes in ERP components other than P300 after CPAP titration[12]. In a study evaluating the effect of titration treatment on the auditory ERP test in OSAS patients, there were no differences between control group N100 latency and P100 amplitudes and shorter N200 amplitudes, while a post-treatment increase in the amplitude of N200 and N100 was reported[12]. Thus, the ERP test can be used as an electrophysiological parameter to reveal brain dysfunction in OSAS[12].

Investigation of the relationship between cognitive function changes and ERP changes after CPAP therapy

The primary aim of the current study was to determine the changes in cognitive functions and electrophysiological potentials after CPAP titration therapy. In this regard, our study found a significant positive correlation between percent change in N100 amplitude and change in sustained attention. In addition, a modest but statistically significant positive correlation was found between percent change in N100 latency and change in long-term recall. A few published studies have reported correlations between cognitive function and N100. These studies have emphasized that N100 potential may reflect a triggering task that filters out other stimuli that may interfere with the maintenance of attention, thus allowing the person to pay attention to stimuli during passive listening and early components like N100 and P200 potentials can change during memory operations[31].These findings support the notion that the N100 component is particularly sensitive to changes in sleepiness and is associated with perceptual discrimination and allocation of attention[12, 32].

The lack of a healthy control group is a limitation of the current study. Furthermore, the sample size studied for the pre-and post-titration comparison was relatively small (n: 17); however, statistically significant changes were still demonstrated. Additionally, care was taken to provide frequent breaks during cognitive evaluation; however, the relatively long duration testing might have affected patient motivation and performance. Moreover, although the intellectual abilities of the patients included in our study were evaluated by clinical interview and MMT, no IQ test was administered to the patients before the test, which can be considered as another limitation.

Conclusion

Cognitive impairment especially in the areas of attention, executive functions, and memory in patients with OSAS increases with the severity of the disease. There is

an overall improvement in cognitive function with CPAP treatment. Studies with larger sample sizes and the inclusion of healthy controls are needed to identify the cognitive domains affected in OSAS and to show improvement with titration therapy.

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