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HEAD AND NECK

Correlation of sleep microstructure with daytime sleepiness and cognitive function in young and middle-aged adults with obstructive sleep apnea syndrome

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Abstract

Purpose To compare microstructural features of sleep in young and middle-aged adults with differing severities of obstructive sleep apnea syndrome (OSAS), and to investigate the relationship between sleep microstructural fragmentation and cognitive impairment, as well as daytime sleepiness, in these patients.

Methods A total of 134 adults with snoring (mean age, 37.54 ± 7.66 years) were classified into four groups based on apnea–hypopnea index: primary snoring, mild OSAS, moderate OSAS, and severe OSAS. Overnight polysomnography was performed to assess respiratory, sleep macrostructure (N1, N2, N3, and R), and sleep microstructure (arousal, cyclic alternating pattern [CAP]) parameters. Cognitive function and daytime sleepiness were assessed using Montreal Cognitive Assessment (MoCA) and Epworth Sleepiness Scale (ESS).

Results As OSAS severity increased, MoCA gradually decreased and ESS gradually increased. N1%, N2%, and N3% sleep were significantly different between the severe OSAS group and the primary snoring, mild OSAS, and moderate OSAS groups (all $P < 0.05$). Overall arousal index, respiratory-related arousal index, CAP time, CAP rate, phase A index, number of CAP cycles, and phase A average time differed significantly in the moderate and severe OSAS groups compared with the mild OSAS and primary snoring groups (all $P < 0.05$). The strongest correlations identified by stepwise multiple regression analysis were between phase A3 index and the MoCA and ESS scores.

Conclusions Sleep microstructure exhibited significant fragmentation in patients with moderate and severe OSAS, which was associated with decreased MoCA and increased ESS scores. This suggests that phase A3 index is a sensitive indicator of sleep fragmentation in OSAS.

Keywords Cyclic alternating pattern · Arousal · Obstructive sleep apnea syndrome · Cognitive function · Daytime sleepiness

Introduction

Obstructive sleep apnea syndrome (OSAS) is an increasingly common sleep disorder [1]. It is characterized by frequent partial or complete collapse of the pharyngeal airway track during sleep. Patients suffering from OSAS experience snoring, sleep structural disturbances, frequent oxygen desaturation events, daytime sleepiness, memory loss, etc., during sleep [2]. Among them, the more common complaints of patients are daytime sleepiness and memory loss.

Electrophysiological studies of the brain of OSAS patients show frequent wakefulness, arousals, and increased transitions of sleep phases which ultimately cause sleep disturbances and disruptions of sleep structure and rhythm [3]. Polysomnography is the primary diagnostic tool for OSAS,

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and its EEG provides the microstructural and macrostructural characteristics of sleep. The macrostructural characteristics of sleep include decreased sleep efficiency, increased proportion of sleep in stages 1 and 2, and decreased proportion of stage 3 and REM sleep phases [4]. The sleep microstructure includes the arousal and the cyclic alternating pattern (CAP). Arousal is a sudden change in the EEG frequency for a short period of at least 3 s. Frequent arousals interrupt the continuity of sleep and eventually lead to sleep disturbance. CAP is a periodic brain electrical rhythm that occurs during non-rapid eye movement sleep which can be used to assess the sleep quality [5]. It is interpreted by analyzing the number and duration of the events during sleep. Studies earlier have shown that the macrostructural features of patients suffering from severe OSAS are significantly different, and the sleep efficiency of OSAS patients is susceptible to various factors [6, 7].

In this study, we explored the relationship between sleep microstructure and cognitive function, as well as daytime sleepiness, to provide insight into the pathological mechanisms of arousal modulation patterns and transient EEG changes in patients with OSAS. We used the Montreal Cognitive Assessment (MoCA) and Epworth Sleepiness Scale (ESS) scales to assess subjective cognitive function and daytime sleepiness and polysomnography (PSG) data to evaluate microstructural sleep patterns (including arousals and CAPs).

Materials and methods

Patients

This cross-sectional observational study was conducted at the sleep center of the Second Affiliated Hospital of Soochow University in Suzhou, China. Of 173 patients with snoring and suspected OSAS referred to the clinic between January 2018 and August 2018. The inclusion criteria were: aged 25–60 years, urban dwelling, and > 9 years of education. Whereas, the exclusion criteria were as follows: diagnosed and treated sleep-related breathing disorder; other sleep disorder, such as insomnia, central sleep apnea, obesity hypoventilation syndrome, restless legs syndrome, rapid eye movement sleep behavior disorders, periodic limb movement disorders, and narcoleptic spectral disorders; mental illness (e.g., depression, anxiety, schizophrenia) or treated with antihistamines, sedative-hypnotics, antidepressants, anti-biotics etc., within the previous 3 months; or neurological malignancies, Alzheimer's disease, or other serious heart, kidney, liver, lung, or brain diseases which affect the quality of life. The following patients were excluded from the study after the exclusion criteria: 17 cases were reluctant to participate or give up halfway, 13 cases were diagnosed with other sleep diseases and nine cases had other diseases. Subsequently, we have enrolled 134 patients.

Sleep questionnaire assessment

All subjects completed ESS and MoCA questionnaires in a quiet, comfortable, and isolated room. The validated Chinese version of the ESS questionnaire [8] (https://epworthsleepinessscale.com) was used, as reported in our previous study [9]. This questionnaire contains eight items, rated on a four-point scale (0–3). The Chinese version of the MoCA questionnaire (Beijing version) (https://www.mocatest.org) was used, which was based on the final English version. MoCA is a 30-point test covering seven cognitive subdomains. When the education duration was < 12 years, one point was added to the total score. MoCA has a sensitivity of 90% and specificity of 87% for evaluating cognitive function [10].

Polysomnography

All patients underwent overnight PSG (Compumedics, Australia) in a quiet room, and all recorded data are manually interpreted by the sleep center's full-time physician. The procedure began at 10:00 p.m. and ended at 6:00 a.m. the following day. The patients were advised to follow their regular sleep pattern, with moderate adjustments, if necessary. Monitoring was considered successful if it continued for ≥ 7 h [11]. Electrophysiological indicators included EEG (F3, F4, C3, C4, O1, O2, A1, and A2 electrodes, placed according to the international 10–20 system), two-channel electrooculography, electromyography (EMG), and electrocardiography. Respiratory-related physiologic indexes included mouth and nose thermistor pressure, nasal airflow, thoracoabdominal breathing movements, arterial oxygen saturation, and snoring index. The apnea–hypopnea index (AHI) was determined for all patients. An obstructive apnea episode was defined as a reduction in the mouth thermistor signal to < 10% of baseline for at least 10 s, with continued or increased respiratory effort. A hypopnea episode was defined as respiratory airflow decreased more than 50% of airflow, and more than 4% of blood oxygen saturation decreased. Additional parameters like, overall arousal index (OAI); lowest oxygen saturation ($LSaO_2$); oxygen saturation less than 90% of the time /total time (TS90%), and body position during sleep were also monitored.

Sleep structure analysis

Sleep macrostructure

Sleep stages were scored according to the American Academy of Sleep Medicine rules [12]. The entire night-time sleep period was divided into these stages: wakefulness,

non-rapid eye movement (REM) phase 1 (N1), non-REM phase 2 (N2), non-REM phase 3 (N3; also known as slow wave sleep [SWS]), and REM phase (R). Conventional sleep macrostructure parameters were determined, including total sleep time (TST), sleep latency, R latency, sleep efficiency, and percentage of time spent in N1, N2, N3, and R stages. The normal values of the percentages of N1, N2, N3 and R stages in the total sleep time in the sleep macrostructure were 2–5%, 45–55%, 15–20%, and 20–25%, respectively.

Sleep microstructure

Arousals EEG (cortical) arousals mark interruptions of sleep, a sign of disrupted sleep architecture. The American Sleep Disorders Association's rules were used to assess arousals [13]. Cortical arousals were defined as abrupt changes in EEG frequency during sleep (e.g., alpha waves, theta waves, frequencies > 16 Hz [but not spindles]) lasting ≥ 3 s and preceded by ≥ 10 s of stable sleep [13]. Arousals during the R stage required an accompanying increase in submental EMG amplitude for ≥ 1 s [13]. We determined the overall arousal index, respiratory-related arousal index, and spontaneous arousal index.

Cyclic alternating patterns CAP analysis was performed manually using the criteria developed by Terzano et al. [14]. A CAP cycle was defined as an activation period (phase A) and subsequent background period (phase B) during NREM sleep. Phase B was defined as the period between two adjacent phase As. Phases A and B could each last for up to 60 s. A complete CAP sequence was composed of ≥ 2 CAP cycles, and all CAP sequences began with a phase A and ended with a phase B. If a CAP did not appear within 60 s, the interval was called a non-CAP (NCAP). That is, if the interval between two adjacent phase As was > 60 s, the CAP sequence ended and the final A phase was considered part of the NCAP [15]. CAP phase As were divided into three subtypes: A1, A2, and A3 [16]. The A1 subtype was mainly represented by low-frequency brainwaves (K-complex waves, slow waves), the A3 subtype predominantly contained high-frequency brainwaves (alpha waves, beta waves), and the A2 subtype was a mixture of low- and high-frequency brainwaves.

We have calculated a number of CAP parameters including: CAP time, CAP rate, A phase index, average phase A and average phase B times. CAP time represented the total duration of all CAP sequences. CAP rate was the ratio of CAP time-to-total NREM sleep time. A index was the number of phase A subtypes per hour of sleep. The average phase A and average phase B times were the average duration of each phase in the CAP sequences.

Statistical analysis

The data are presented as mean ± standard deviation unless indicated otherwise. All data were analyzed using Statistical Products and Services Solutions (SPSS, 22nd version). The macrostructural and microstructural sleep characteristic parameters of the four groups were compared using one-way analysis of variance or Mann–Whitney *U* test. Pair-wise group comparisons were subsequently performed using Fisher's least squares difference post hoc test. Linear regression and stepwise multiple regression analyses were used to assess correlations between MoCA scores and ESS scores and various sleep macrostructure and microstructure parameters. Rates were compared using the Chi-square test. When the *P* value was < 0.05, the difference was considered statistically significant.

Results

The 134 patients in the study had a mean age of 37.54 ± 7.66 years and body mass index of 26.17 ± 2.81 kg/m^2. They were divided into four groups, as recommended by the Chinese Medical Association [17]: primary snoring (AHI < 5 events/h; $n = 25$), mild OSAS (AHI 5–14.9 events/h; $n = 28$), moderate OSAHS (AHI 15–30 events/h; $n = 26$), and severe OSAHS (AHI > 30 events/h; $n = 55$). The majority of patients (60.45%; $n = 81$) had moderate-to-severe OSAS.

Table 1 shows characteristics of patients in each group. There were no significant differences in gender ($P = 0.185$) or age ($P = 0.179$) between the four groups. The BMI, however, was significantly different between groups ($P < 0.001$); the BMI was higher in the severe OSAS group than each of the other groups.

Sleep questionnaires

The MoCA and ESS scores were statistically different among the four groups ($P < 0.01$) (Table 1). In general, MoCA scores decreased as the OSAS severity increased. This result did not appear to be affected by education level, as the number of years of education did not differ between groups ($P = 0.822$). The ESS scores were consistent with the percentage of patients with daytime sleepiness. The mean ESS score of the severe OSAS group was 13.50 ± 4.32 ($P < 0.01$), which was higher than that of the other groups.

Polysomnography

Sleep macrostructure

As shown in Table 2, the percentage of N3 time was significantly lower in the severe OSAS group than in the

Table 1 Demographic and clinical characteristics of patients with primary snoring or obstructive sleep apnea syndrome

Characteristic	Primary snoring ($n=25$)	Mild OSAS ($n=28$)	Moderate OSAS ($n=26$)	Severe OSAS ($n=55$)	P value
Age (years)	33.30 ± 3.92	38.15 ± 8.86	37.47 ± 7.47	38.58 ± 7.67$^{☆}$	0.179
Sex, % males	88.0	92.9	92.3	96.4	0.185
BMI (kg/m^2)	24.81 ± 2.61	25.44 ± 1.99	24.30 ± 2.53	27.58 ± 2.67$^{★▲■}$	< 0.001
Morning blood pressure (mmHg)					
Systolic	115.80 ± 12.63	121.31 ± 11.64	121.00 ± 12.21	128.31 ± 12.02$^{★}$	0.020
Diastolic	81.60 ± 7.04	87.00 ± 8.89	83.00 ± 7.22	90.11 ± 8.53$^{★□}$	0.025
Hypertension, *n* (%)	7 (28.0)	11 (39.3)	13 (50.0)	28 (50.9)	0.049
Common symptoms, *n* (%)					
Daytime sleepiness	13 (52.0)	15 (53.6)	16 (61.5)	36 (65.5)	0.185
Poor memory	5 (20.0)	5 (17.9)	7 (26.9)	17 (30.9)$^{△}$	0.182
Education (years)	12.0 (6.0)	14.0 (4.0)	14.0 (4.0)	15.0 (5.0)	0.822
MoCA score	27.0 (2.0)	26.0 (2.0)$^{★}$	25.0 (2.0)$^{★}$	25.5 (2.0)$^{★△}$	< 0.001
ESS score	7.20 ± 3.68	11.15 ± 5.13$^{☆}$	12.80 ± 5.78$^{★△}$	13.50 ± 4.32$^{★▲}$	< 0.001

Data are mean ± SD or median (interquartile range) unless otherwise indicated

BMI body mass index, *ESS* Epworth Sleepiness Scale, *MoCA* Montreal Cognitive Assessment, *OSAS* obstructive sleep apnea–hypopnea syndrome

$^{☆}P<0.05$ vs. primary snoring group, $^{★}P<0.01$ vs. primary snoring group, $^{△}P<0.05$ vs. mild OSAS group, $^{▲}P<0.01$ vs. mild OSAS group, $^{□}P<0.05$ vs. moderate OSAS group, $^{■}P<0.01$ vs. moderate OSAS group

Table 2 Sleep macrostructure parameters in patients with primary snoring or obstructive sleep apnea syndrome

Parameter	Primary snoring ($n=25$)	Mild OSAS ($n=28$)	Moderate OSAS ($n=26$)	Severe OSAS ($n=55$)	P value
TST (min)	412.10 ± 84.90	424.81 ± 69.73	449.93 ± 75.07	445.96 ± 74.40	0.469
Sleep efficiency (%)	85.7 (20.5)	89.3 (21.0)	87.9 (15.7)	88.1 (15.6)	0.837
Sleep latency (min)	8.3 (16.0)	4.5 (16.5)	5.5 (8.5)	2.75 (7.9)	0.283
Wakefulness (min)	44.5 (116.0)	52.0 (88.8)	40.0 (89.5)	47.5 (69.8)	0.834
N1 (%)	7.72 ± 3.53	11.63 ± 5.25	11.64 ± 8.43	14.66 ± 9.71$^{★△}$	0.013
N2 (%)	51.21 ± 8.07	49.72 ± 9.72	50.12 ± 11.44	56.75 ± 11.56$^{☆▲□}$	0.018
N3 (%)	19.12 ± 5.56	17.61 ± 7.67	16.20 ± 7.12	8.12 ± 6.51$^{★▲■}$	< 0.001
R (%)	21.97 ± 4.36	21.03 ± 6.28	19.61 ± 6.88$^{☆}$	20.37 ± 5.63$^{☆}$	0.060
R latency (min)	77.8 (68.4)	79.0 (85.5)	109.0 (105.0)$^{☆}$	109.8 (89.8)$^{☆}$	0.048
AHI (n/h)	2.61 ± 1.66	9.41 ± 2.51$^{★}$	23.25 ± 5.04$^{★▲}$	53.90 ± 16.21$^{★▲■}$	< 0.001
ODI (次/h)	2.52 ± 2.80	7.37 ± 2.89	18.70 ± 6.23$^{★▲}$	47.05 ± 16.20$^{★▲■}$	< 0.001
TS90% (%)	0.00 ± 0.03	0.78 ± 1.23	5.95 ± 5.70	23.34 ± 19.51$^{★▲■}$	< 0.001
LSaO2 (%)	91.28 ± 1.67	86.96 ± 3.13$^{★}$	78.77 ± 7.83$^{★▲}$	71.51 ± 8.94$^{★▲■}$	< 0.001

Data are presented as mean ± SD or median (interquartile range)

AHI apnea–hypopnea index, *N* non-rapid eye movement sleep, *OSAS* obstructive sleep apnea syndrome, *R* rapid eye movement sleep, *TST* total sleep time, *OAI* overall arousal index, $LSaO_2$ lowest oxygen saturation, *TS90%* oxygen saturation less than 90% of the time/total time

$^{☆}P<0.05$ vs primary snoring group, $^{★}P<0.01$ vs primary snoring group, $^{△}P<0.05$ vs. mild OSAS group, $^{▲}P<0.01$ vs. mild OSAS group, $^{□}P<0.05$ vs. moderate OSAS group, $^{■}P<0.01$ vs. moderate OSAS group

primary snoring, mild OSAS, and moderate OSAS groups ($P<0.01$ for all comparisons). In contrast, the N1 and N2 sleep percentages were higher in the severe OSAS group than in the other groups. R latency also differed significantly between the four groups ($P<0.048$). These findings indicate that sleep macrostructure worsened as OSAS severity increased, with severely disturbed macrostructure in patients with severe OSAS. With the increase of the severity of OSAS, the values of parameters like AHI, ODI, TS90% and LSaO2 increased gradually ($P<0.01$).

Sleep microstructure

Arousals As depicted in Table 3, the overall arousal index and respiratory-related arousal index differed between the four groups ($P<0.01$ for both), increasing as the severity of OSAS increased. Respiratory-related arousal index was significantly different in the mild OSAS group than in the primary snoring group ($P<0.01$). However, the spontaneous arousal index did not differ significantly between groups ($P<0.168$).

Cyclic alternating patterns As shown in Table 3, the total CAP time and overall CAP rate in the moderate and severe OSAS groups were significantly higher than in both the primary and mild groups ($P<0.01$ for all). Furthermore, CAP rates during N1 and N2 sleep stages increased with increasing severity of OSAS ($P<0.01$ for both). Moreover, the N1 CAP rate for all three OSAS groups was significantly higher than for the primary snoring group. However, CAP rates during N3 sleep did not differ among groups ($P=0.457$). Similarly, phase A index values in the moderate and severe OSAS groups were significantly higher than in the primary snoring and mild OSAS groups ($P<0.01$ for all). Phase A1 and A2 indices in the severe group were significantly higher than in the other three groups. Moreover, phase A3 index in both the moderate and severe OSAS groups was significantly higher than in the primary snoring group and mild groups ($P<0.01$ for all). Phase A3 index was also higher in the moderate OSAS group than in the severe group ($P<0.01$). The average phase A duration in the severe OSAS group was significantly higher than in the other three groups ($P<0.01$), whereas the phase B average duration in the severe OSAS group was higher than in both the primary snoring and mild OSAS groups ($P<0.05$ for both). The average phase A2 duration was higher in the severe OSAS group than in the primary snoring ($P<0.01$) and mild OSAS ($P<0.05$) groups, and the average phase A3 duration was higher in the severe OSAS group than in the other three groups ($P<0.01$ for all).

Correlation analyses

Linear and stepwise multiple regression analyses were performed to assess correlations of MoCA and ESS scores with sleep macrostructure (N1, N2, N3, and R phases) and microstructure (CAP and arousal-related parameters). The results are shown in Table 4. The strongest correlations were noted between the MoCA score and phase A3 index ($r=-0.329$, $b=-0.352$, $P<0.01$) and between the ESS score and phase A3 index ($r=0.357$, $b=0.366$, $P<0.01$).

Table 3 Sleep microstructure parameters in patients with primary snoring or obstructive sleep apnea syndrome

Parameter	Primary snoring ($n=25$)	Mild OSAS ($n=28$)	Moderate OSAS ($n=26$)	Severe OSAS ($n=55$)	*P* value
Overall arousal index (n/h)	5.8 (6.5)	10.5 (9.0)	16.9 (13.2)★▲	35.7 (30.5)★▲■	<0.001
Respiratory-related arousal index (n/h)	0.5 (2.0)	3.6 (3.7)★	10.0 (15.3)★▲	29.9 (26.9)★▲■	<0.001
Spontaneous arousal index (n/h)	5.71 ± 3.53	6.52 ± 5.25	6.65 ± 3.08	5.15 ± 3.21□	0.168
CAP time (min)	73.29 ± 32.44	102.23 ± 37.79	153.27 ± 52.73★▲	231.34 ± 93.17★▲■	<0.001
CAP rate (%)	26.1 (11.8)	28.3 (10.9)	41.8 (31.5)★▲	72.1 (32.8)★▲■	<0.001
N1 CAP rate (%)	19.36 ± 12.89	34.82 ± 17.07★	35.07 ± 23.85★	49.51 ± 23.12★▲□	<0.001
N2 CAP rate (%)	29.73 ± 12.20	37.23 ± 14.57	53.09 ± 16.48★▲	73.98 ± 24.59★▲■	<0.001
N3 CAP rate (%)	7.7 (8.3)	5.3 (11.8)	9.7 (13.3)	11.35 (41.8)	0.457
Phase A index (n/h)	30.12 ± 12.33	37.67 ± 14.09	50.95 ± 19.42★▲	61.42 ± 21.18★▲	<0.001
Phase A1 index (n/h)	6.3 (13.1)	10.1 (14.8)	9.1 (19.2)	3.25 (7.5)☆▲■	<0.001
Phase A2 index (n/h)	9.59 ± 4.81	8.04 ± 5.05	8.39 ± 4.08	6.13 ± 5.25☆△□	0.031
Phase A3 index (n/h)	11.8 (11.5)	16.1 (13.3)	26.4 (15.3)★▲	50.6 (28.4)★▲■	<0.001
Number of CAP cycles	160.30 ± 76.70	207.69 ± 82.53	298.20 ± 112.85★▲	352.08 ± 147.79★▲	<0.001
A phase average time (s)	10.6 ± 1.90	12.82 ± 2.66	13.07 ± 2.49☆	16.85 ± 3.53★▲■	<0.001
A1 phase average time (s)	7.09 ± 1.08	7.04 ± 1.75	7.01 ± 2.46	7.09 ± 2.39	0.641
A2 phase average time (s)	10.9 (4.0)	13.0 (2.9)	13.2 (4.9)	14.2 (3.5)★△	0.003
A3 phase average time (s)	13.48 ± 2.56	16.11 ± 2.39	14.85 ± 2.23	18.13 ± 3.46★▲■	<0.001
B phase average time (s)	14.8 (6.5)	15.7 (5.2)	15.7 (3.2)	17.5 (7.4)☆△	0.024

Data are presented as mean ± SD or median (interquartile range)

CAP cyclic alternating pattern, *N* non-rapid eye movement sleep, *OSAS* obstructive sleep apnea–hypopnea syndrome

☆$P<0.05$ vs. primary snoring group, ★$P<0.01$ vs. primary snoring group, △$P<0.05$ vs. mild OSAS group, ▲$P<0.01$ vs. mild OSAS group, □$P<0.05$ vs. moderate OSAS group, ■$P<0.01$ vs. moderate OSAS group

Table 4 MoCA and ESS score correlations with sleep macrostructure and microstructure parameters

Parameter	MoCA score		ESS score	
	r	*P* values	*r*	*P* values
TST (min)	0.085	0.331	0.119	0.176
Sleep efficiency (%)	0.113	0.193	−0.037	0.671
N1 (%)	−0.216	0.012*	0.157	0.073
N2 (%)	−0.005	0.950	0.074	0.400
N3 (%)	0.125	0.151	−0.260	0.003**
R (%)	0.254	0.003**	−0.122	0.162
Overall arousal index (n/h)	−0.299	< 0.001**	0.344	< 0.001**
Respiratory-related arousal index (n/h)	−0.297	0.001**	0.357	0.000**
Spontaneous arousal index (n/h)	−0.003	0.969	−0.067	0.444
CAP time (min)	−0.225	0.009**	0.344	< 0.001**
CAP rate (%)	−0.288	< 0.001**	0.345	< 0.001**
Phase A index (n/h)	−0.217	0.012*	0.225	0.009**
Phase A1 index (n/h)	0.120	0.167	−0.134	0.126
Phase A2 index (n/h)	0.156	0.072	−0.200	0.021*
Phase A3 index (n/h)	−0.329	< 0.001**	0.357	< 0.001**
Number of CAP cycles	−0.164	0.058	0.230	0.008**
Phase A average time (s)	−0.324	< 0.001**	0.269	0.002**
Phase B average time (s)	−0.088	0.311	0.233	0.007**

CAP cyclic alternating pattern, *N* non-rapid eye movement sleep, *r* correlation coefficient, *R* rapid eye movement sleep, *TST* total sleep time

*Significant at the 0.05 level (two-tailed)

**Significant at the 0.01 level (two-tailed)

Discussion

This observational study was conducted to understand the microstructural sleep characteristics of patients with OSAS and the relationship between these characteristics and clinical symptoms (daytime sleepiness and cognitive impairment). Our main findings were that arousal and CAP-related parameters gradually increased as the severity of OSAS increased and that the phase A3 index was correlated with the ESS and MoCA scores. These findings suggest that altered sleep microstructure may reflect one of the pathological mechanisms of sleep disorders in patients with OSAS and is associated with cognitive dysfunction and excessive daytime sleepiness in patients with OSAS.

The sleep EEG is the primary diagnostic tool that provides not only macrostructural sleep information regarding sleep phases but also information about microstructural features, such as CAP [18]. CAP is a periodic EEG activity that is translated into larger and smaller arousal levels (A and B, respectively) and reflects arousal instability [19]. As sleep microstructure can provide a complete description of transient and dynamic EEG activities during sleep, microstructural sleep analysis has received increasing attention by researchers [20]. The generation of CAP is not restricted by EEG activity, as it reflects ongoing autonomic activities and behavioral functions, and it can be detected in all age groups [16]. CAP is manifested as NREM sleep periodic EEG activity.

In the current study, we found that the overall and respiratory-related arousal indices, CAP time, CAP rate, phase A index, number of CAP cycles, and average duration of phase A were significantly higher in the moderate and severe OSAS groups than in the primary snoring and mild OSAS groups. However, the spontaneous arousal index and average duration of phase B were similar between the four groups. In their study of 21 patients with CAP-dominant obstructive sleep-disordered breathing, Thomas et al. [21] found that CAP was associated with motor control and autonomic mechanisms of repeated nocturnal apneas. Mariani et al. [22] found that a large number of CAPs reflected cortical activation after repeated nocturnal apnea events, which resulted in increased arousals during sleep. As CAP provides an in-depth understanding of the complexity of sleep stage arousals, most parameters related to CAP and arousals differ in patients with OSAS compared with individuals with primary snoring.

Another important finding of this study was that MoCA and ESS scores were associated with the overall arousal index, respiratory-related arousal index, CAP time, CAP rate, phase A index, phase A3 index, and average duration of phase A in correlation analyses. Furthermore, in stepwise multiple regression analysis, the phase A3 index

was the characteristic most closely associated with MoCA and ESS scores. Previously, Della et al. [23] reported that the CAP time and rate of 17 patients with transient global amnesia were significantly lower than those of 17 age-matched healthy controls; these findings differed from our findings in patients with OSAS. However, in their study of 42 children with OSAS, Bruni et al. [24] found a positive correlation between fluid reasoning and the CAP rate. In our current study, we also detected a correlation between MoCA score and the CAP rate. Previous studies have found that daytime sleepiness in patients with OSAS is significantly correlated with phase A3, CAP rate, and arousals [25], which is consistent with the results of our current study.

Our findings suggest that pathophysiological mechanisms in OSAS involve altered regulation of sleep structure. In particular, the respiratory-related arousal index and phase A3 index can play an important role in sleep disorders in patients with OSAS. Moreover, an increased phase A3 index was significantly correlated with daytime sleepiness and cognitive impairment in patients with OSAS. These findings are consistent with those of previous studies. Ferri et al. [26] concluded that increased phase A1 was associated with higher cognitive function, whereas increased phase A3 was associated with lower cognitive function. Another study reported that children with a higher proportion of phase A1 and SWS had higher cognitive function [24].

Changes in CAP parameters are not only a problem in OSAS, but they are also found in conditions with altered circadian rhythms and periodic EEG arousals, such as insomnia [27], migraines [28], and seizures [29]. In addition to physiological changes, CAP parameters can also change in response to external and internal factors, such as depression, epilepsy, periodic limb movement, circadian rhythm limitation, noise, and ambient temperature.

The main limitations of this study were its small sample size, single-center design, and inclusion of only young and middle-aged patients. However, the age range represents real-world circumstances, as there is a high prevalence of OSAS in these age groups. The study provides useful information, although the generalizability of the results is unclear.

In conclusion, our results showed that CAP and arousal parameters gradually increase with the severity of OSAS, and the amount of change of these parameters is more obvious than that of macrostructural sleep parameters. We also found that CAP and arousal parameters—especially the phase A3 index—are closely related to daytime sleepiness and cognitive function in patients with OSAS. More research is required to further evaluate the relationship between CAP parameters and severity of OSAS, as well as clinical symptoms in patients with OSAS.

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Compliance with ethical standards

Conflict of interest Author Chen Rui has received research grants from the Natural Science Foundation of China and the Suzhou Clinical Key Disease Diagnosis and Treatment Technology Special. Author Chen Rui declares that she has no conflict of interest.

Ethical approval The study was approved by our hospital's institutional ethics committee (Batch number: JD-LK-2018-006-01).

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Heinzer R, Vat S, Marques-Vidal P et al (2015) Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med 3(4):310–318
2. Peppard PE, Young T, Barnet JH et al (2013) Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol 177(9):1006–1014
3. Jordan AS, Mcsharry DG, Malhotra A (2014) Adult obstructive sleep apnoea. Lancet 383(9918):736–747
4. Chen R, Xiong KP, Huang JY et al (2011) Neurocognitive impairment in Chinese patients with obstructive sleep apnoea hypopnoea syndrome. Respirology 16(5):842–848
5. Zeitlhofer J, Gruber G, Anderer P et al (1997) Topographic distribution of sleep spindles in young healthy subjects. J Sleep Res 6(3):149–155
6. Weichard AJ, Walter LM, Hollis SL et al (2016) Association between slow wave activity, cognition and behaviour in children with sleep disordered breathing. Sleep Med 25:49–55
7. Gurbani N, Verhulst SL, Tan C et al (2017) Sleep complaints and sleep architecture in children with idiopathic central sleep apnea. J Clin Sleep Med 13(6):777–783
8. Johns MW (1991) A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 14(6):540–545
9. Reynolds CF (1987) Sleep deprivation as a probe in the elderly. Arch Gen Psychiatry 44(11):982
10. Nasreddine ZS, Phillips NA, Bédirian V et al (2005) The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 53(4):695–699
11. Chen R, Xiong KP, Lian YX et al (2011) Daytime sleepiness and its determining factors in Chinese obstructive sleep apnea patients. Sleep Breath 15(1):129–135
12. Iber C, Ancoli-Israel S, Chesson AL, American Academy of Sleep Medicine et al (2007) The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. American Academy of Sleep Medicine, Westchester
13. Anonymous (1992) EEG arousals: scoring rules and examples: a preliminary report from the sleep disorders atlas task force of the American Sleep Disorders Association. Sleep 15(2):173
14. Terzano MG, Parrino L, Smerieri A (2001) Atlas, rules, and recording techniques for the scoring of cyclic alternating pattern (CAP) in human sleep. Sleep Med 3(2):187–199

15. Smerieri A, Parrino L, Agosti M et al (2007) Cyclic alternating pattern sequences and non-cyclic alternating pattern periods in human sleep. Clin Neurophysiol 118(10):2305–2313
16. Parrino L, Ferri R, Bruni O et al (2012) Cyclic alternating pattern (CAP): the marker of sleep instability. Sleep Med Rev 16(1):0–45
17. Chinese Medical Association, Sleep Breathing Disorders Group (2002) Diagnostic and therapic manual for obstructive sleep apnea–hypopnea syndrome. Chin J Tuberc Respir Dis 25:195–198
18. Simor P, Bódizs R, Horváth K et al (2013) Disturbed dreaming and the instability of sleep: altered nonrapid eye movement sleep microstructure in individuals with frequent nightmares as revealed by the cyclic alternating pattern. Sleep 36(3):413–419
19. Mariani S, Manfredini E, Rosso V et al (2012) Efficient automatic classifiers for the detection of A phases of the cyclic alternating pattern in sleep. Med Biol Eng Comput 50(4):359–372
20. Terzano MG, Parrino L, Rosa A et al (2002) CAP and arousals in the structural development of sleep: an integrative perspective. Sleep Med 3(3):221–229
21. Thomas RJ, Terzano MG, Parrino L et al (2004) Obstructive sleep-disordered breathing with a dominant cyclic alternating pattern—a recognizable polysomnographic variant with practical clinical implications. Sleep 27:229–234
22. Mariani S, Manfredini E, Rosso V et al (2011) Characterization of A phases during the cyclic alternating pattern of sleep. Clin Neurophysiol 122(10):0–2024
23. Marca GD, Mazza M, Losurdo A et al (2013) Sleep modifications in acute transient global amnesia. J Clin Sleep Med 9(9):921–927
24. Bruni O, Kohler M, Novelli L et al (2012) The role of NREM sleep instability in child cognitive performance. Sleep 35(5):649–656
25. Selda K, Tugce BN, Murat A et al (2018) Cyclic alternating pattern in obstructive sleep apnea patients with versus without excessive sleepiness. Sleep Disord 2018:1–7
26. Ferri R, Drago V, Aricò D et al (2010) The effects of experimental sleep fragmentation on cognitive processing. Sleep Med 11(4):0–385
27. Manconi M, Ferri R, Miano S et al (2017) Sleep architecture in insomniacs with severe benzodiazepine abuse. Clin Neurophysiol 128(6):875–881
28. Nayak C, Sinha S, Nagappa M et al (2015) Study of sleep microstructure in patients of migraine without aura. Sleep Breath 20(1):1–7
29. Giorgi FS, Maestri M, Guida M et al (2017) Cyclic alternating pattern and interictal epileptiform discharges during morning sleep after sleep deprivation in temporal lobe epilepsy. Epilepsy Behav 73:131–136