Electroencephalography Theta/Beta Ratio Decreases in Patients with Severe Obstructive Sleep Apnea

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Purpose: Accumulating evidence suggests that theta/beta ratio (TBR), an electroencephalographic (EEG) frequency band parameter, might serve as an objective marker of executive cognitive control in healthy adults. Obstructive sleep apnea (OSA) has a detrimental impact on patients’ behavior and cognitive performance while whether TBR is different in OSA population has not been reported. This study aimed to explore the difference in relative EEG spectral power and TBR during sleep between patients with severe OSA and non-OSA groups.

Patients and Methods: 142 participants with in-laboratory nocturnal PSG recording were included, among which 100 participants suffered severe OSA (apnea hypopnea index, AHI > 30 events/hour; OSA group) and 42 participants had no OSA (AHI ≤ 5 events/h; control group). The fast Fourier transformation was used to compute the EEG power spectrum for total sleep duration within contiguous 30-second epochs of sleep. The demographic and polysomnographic characteristics, relative EEG spectral power and TBR of the two groups were compared.

Results: It was found that the beta band power during NREM sleep and total sleep was significantly higher in the OSA group than controls (p < 0.001, p = 0.012, respectively), and the theta band power during NREM sleep and total sleep was significantly lower in the OSA group than controls (p = 0.019, p = 0.014, respectively). TBR during NREM sleep, REM sleep and total sleep was significantly lower in the OSA group compared to the control group (p < 0.001 for NREM sleep and total sleep, p = 0.015 for REM sleep). TBR was negatively correlated with AHI during NREM sleep (r=−0.324, p < 0.001) and total sleep (r=−0.312, p < 0.001).

Conclusion: TBR was significantly decreased in severe OSA patients compared to the controls, which was attributed to both increased beta power and decreased theta power. TBR may be a stable EEG-biomarker of OSA patients, which may accurately and reliably identify phenotype of patients.

Keywords: sleep electroencephalography, spectral power, frequency band ratio, theta/beta ratio, OSA

Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder characterized by repetitive pauses (apneas) or reductions in airflow amplitude (hypopneas) attributed to the collapsibility of the upper airway during sleep. A growing number of studies indicate that OSA, especially moderate-to-severe OSA, has a detrimental impact on patients’ behavior and cognitive performance. These adverse effects might be driven by disrupted restorative functions of nighttime sleep and reduced oxygen delivery resulting in neuronal damage. Continuous positive airway pressure (CPAP) can reverse cognitive deficits associated with OSA and improve occupational well-being and job productivity of the patients. Moreover, mild patients even obtain neurocognitive enhancements upon timely treatment. Hence, it is necessary to objectively identify cognitive impairments in OSA patients to minimize their impact and maximize their reversibility.
Currently, clinical evaluation of cognitive impairments often relies on subjective questionnaires which are not strongly and consistently related to disease severity (apnea hypopnea index, AHI and oxygen saturation indices), thus limiting the ability to draw conclusions on the association. Therefore, accurate and reliable objective evaluation methods and indicators are urgently needed to evaluate cognitive impairments of OSA patients.

Electroencephalogram (EEG) recordings as an objective measure can be quantitatively analyzed to reveal variations in brain activity. Previous quantitative EEG (qEEG) studies in OSA patients demonstrated a significantly slow brain activity during wakefulness over all cortical regions, suggesting lower levels of vigilance or a general brain dysfunction. Several studies exploring sleep EEG focused on specific EEG attributes of OSA patients, such as spindles, theta or delta activity, but the results were inconsistent. Consequently, how OSA alters the overnight electrical behavior of the brain remains unclear.

It has been reported that band ratio measures are more stable than either absolute or relative measures of individual frequency band power, with high test–retest reliability within individuals. The most common clinical application of band ratio measures is theta/beta ratio (TBR), which is used to investigate executive cognitive control, more specifically attentional control in healthy adults and also attention-deficit hyperactivity disorder (ADHD). Previous studies reported a relatively increased theta wave and decreased beta wave of awake-EEG in ADHD, and TBR was proposed as a potential diagnostic biomarker for the disorder. Slow theta waves are linked to subcortical brain regions involved in affective processes, whereas fast beta activity that is argued to reside at the thalamo-cortical and cortico-cortical level is associated with cognitive control processes. Since OSA has been reported to be associated with cognitive impairments, it is unknown whether the cognition-related brain damage can be indicated by EEG and there is no relevant study on the characteristics of TBR in patients with OSA.

The purpose of the current study was to assess electrocortical profiles during sleep in adults with severe OSA. It was hypothesized that OSA subjects were characterized by higher fast waves, lower slow waves and lower TBR during sleep compared to the controls.

**Methods**

**Participants**

A consecutive series of participants from the Sleep Medical Center of Beijing Tsinghua Changgung Hospital in Beijing, China, between January 2017 and August 2021 were recruited. Polysomnography (PSG) was used as the diagnostic standard of OSA. Inclusion criteria: aged 40–65 years; AHI > 30 events/hour for OSA patients (n = 100) or AHI ≤ 5 events/h for controls (n = 42). These cut-offs were used to ensure the maximum difference between the control and the OSA groups while maximizing the number of subjects in each group. Exclusion criteria: (i) Severe complications affecting sleep, such as cancer, chronic pain, etc.; (ii) Previous diagnosis of major psychiatric disorders or taking drugs for the treatment of mental diseases, such as depression, anxiety disorder, schizophrenia, etc.; (iii) History of uvulopalatopharyngoplasty; (iv) Suspected of other major sleep disorders, such as insomnia, restless leg syndrome, rapid eye movement sleep behavior disorder, circadian rhythm sleep disorder or narcolepsy; (v) Have a clear history of Parkinson’s disease, epilepsy, stroke and other brain diseases affecting EEG; (vi) Significant artifacts in EEG data. All participants were interviewed and evaluated by doctors. Written informed consent was obtained from all participants prior to inclusion in the study. This study was performed following the principle of the Declaration of Helsinki, and the protocol had been approved by the ethics committee of Beijing Tsinghua Changgung Hospital, Tsinghua University. All experiments were performed in accordance with relevant guidelines and regulations.

**Overnight Polysomnography**

All the participants underwent in-laboratory nocturnal PSG recording. Standard PSG recordings included six electroencephalogram leads (F3, F4, C3, C4, O1, and O2), one electrocardiography channel, two electrooculogram channels (E1-M2 and E2-M2), and three electromyography channels (chin and both anterior tibialis muscles), and were conducted according to the recommendations of the American Academy of Sleep Medicine (AASM). PSG was performed using SOMNO systems (SOMNO medics Corporation, Germany), and PSG results were scored based on the criteria in the...
AASM2012 manual. Two board-certified PSG technologists completed the interscorer. An apnea event was defined as complete cessation of airflow lasting for at least 10s, and a hypopnea event was defined as a reduction in airflow of more than 50% lasting at least 10s or a less significant reduction in the airflow in the presence of arousal or oxygen desaturation of at least 3%. AHI was calculated as the sum of the numbers of apneas, hypopneas and arousal each hour of sleep.

Power Spectral Analysis of EEG
Raw EEG recordings were sampled at 128 Hz. The EEG was inspected visually, and epochs with excessive noise, drift or unstable connection were removed. The primary EEG channel (C4-A1) was exported and was digitally band-pass filtered from 1 to 20 Hz to remove any low- or high-frequency artifacts. Data on changes in sleep stages were then exported as plain text and automatically matched with EEG recordings by synchronizing with the clinically scored sleep onset time. The power spectral density of EEG recording was estimated by applying Welch’s method. A 5s Hanning window with 50% overlap and fast Fourier transform were applied, and a frequency resolution of 0.2 Hz was set. These 0.2 Hz frequency bins were subsequently summed within 5 frequency bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), sigma (12–15 Hz), and beta (15–20 Hz). The relative spectral power was determined as the frequency band power divided by total power in different sleep stages. For the present analysis, the data during total sleep, NREM sleep, and REM sleep were analyzed. TBR was defined as the ratio of relative theta band (4–8 Hz) power and relative beta band (15–20 Hz) power. TAR referred to the ratio of relative theta band (4–8 Hz) power and relative alpha band (8–12 Hz) power. A global measure of EEG slowing was also calculated which is reflected by the ratio of slow frequencies to fast frequencies (delta + theta)/(alpha + sigma + beta).

Statistical Analysis
Data were first tested for normality and equal variance, which were presented as mean ± standard deviation or n (%) values unless indicated otherwise. All data were analyzed using Statistical Products and Services Solutions (SPSS, 22.0 version). Chi-square test was performed for categorical variables, and two-tailed independent t-test of variance or analysis of covariance was used to compare the demographics, PSG characteristics, relative spectral power, frequency band ratios (TAR and TBR) and EEG slowing between the two groups. Cohen’s d was calculated to reflect the difference in effect between OSA and control group (Stata, 16.0 version). Pearson correlation analysis was performed to assess the correlation between AHI, arousal index (ArI) and relative spectral power. SPSS 22.0 was used to conduct analyses except the calculation of Cohen’s d. When the P value was <0.05, the difference was considered statistically significant.

Results
Demographic and PSG Characteristics of the Participants
A total of 142 participants were included in the present study. The demographic and clinical characteristics of the participants are presented in Table 1. The mean age of the participants in the OSA group and control group was 51.5 ± 7.2 years and 52.1 ± 8.0, respectively, without significant difference. There were also no significant differences in sex and Epworth sleepiness scale (ESS) scores between the two groups. As expected, the groups differed in body mass index (BMI), AHI, AI, hypopnea index (HI) and ArI and all values were higher in the OSA group compared to the controls. The OSA group was at higher risk for hypertension. We found no significant differences in the prevalence of diabetes, arrhythmia and coronary artery diseases between the two groups. The lowest oxygen saturation (LSaO2) was significantly lower in the OSA group compared to the controls. PSG data indicated that there were significant differences in the ratio of N1, N2 and REM sleep and sleep latency between the two groups except the ratio of N3, total sleep and sleep efficiency. The polysomnographic characteristics of the participants are presented in Table 2.
Comparison of Relative Spectral Power and Frequency Band Ratios Between the Two Groups

In the comparison between groups for the relative spectral power during NREM sleep (Table 3) and total sleep (Table 3), the beta band power was significantly higher in the OSA group (p < 0.001, Cohen’s d (d) = 0.461 for NREM sleep; p = 0.012, d = 0.457 for total sleep, respectively), and the theta band power was significantly lower in the OSA group (p = 0.019, d = 0.455 for NREM sleep; p = 0.014, d = 0.443 for total sleep, respectively) than in the control group (Figure 1). Thus, TBR was significantly lower in the OSA group compared to the controls (p < 0.001, d = 0.805 for NREM sleep and p < 0.001, d = 0.815 for total sleep) (Figure 2). There were also significant differences between the OSA group and control group in TBR during REM sleep (p = 0.015, d = 0.539). In addition, OSA patients showed significantly higher delta power (p = 0.032, d = 0.397) and lower theta power (p = 0.001, d = 0.600) during REM sleep compared to the controls (Table 3). We found no difference in the EEG slowing ratio between the two groups in NREM (p = 0.812, d = 0.044), REM (p = 0.240, d = 0.217) and total sleep (p = 0.711, d = 0.068), although the mean value of OSA was higher than that of controls.

### Table 1 Demographic and Clinical Characteristics of All the Participants

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control (n = 42)</th>
<th>OSA (n = 100)</th>
<th>t/χ²-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>52.1 ± 8.0</td>
<td>51.5 ± 7.2</td>
<td>0.508⁹</td>
<td>0.612</td>
</tr>
<tr>
<td>Male (n, %)</td>
<td>19, 45.2%</td>
<td>63, 63%</td>
<td>3.824⁹</td>
<td>0.051</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.3 ± 3.7</td>
<td>28.8 ± 4.3</td>
<td>−4.53⁵</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESS</td>
<td>4.93 ± 5.4</td>
<td>6.8 ± 4.8</td>
<td>−1.94⁴</td>
<td>0.054</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (n, %)</td>
<td>10, 23.8%</td>
<td>53, 53%</td>
<td>10.21¹</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes (n, %)</td>
<td>5, 11.9%</td>
<td>21, 21%</td>
<td>1.63</td>
<td>0.201</td>
</tr>
<tr>
<td>CAD (n, %)</td>
<td>2, 4.8%</td>
<td>4, 4%</td>
<td>0.04²</td>
<td>0.837</td>
</tr>
<tr>
<td>Arrhythmia (n, %)</td>
<td>2, 4.8%</td>
<td>9, 9%</td>
<td>0.74³</td>
<td>0.389</td>
</tr>
</tbody>
</table>

Notes: Data are expressed as mean ± standard deviation or n (%) values; ⁹Was for independent t-test; ¹Was for χ² test.

Abbreviations: OSA, obstructive sleep apnea; BMI, body mass index; ESS, Epworth Sleepiness Scale; CAD, coronary artery disease.

### Table 2 Polysomnographic Characteristics of All the Participants

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control (n = 42)</th>
<th>OSA (n = 100)</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHI (events/h)</td>
<td>3.0 ± 2.0</td>
<td>61.1 ± 18.2</td>
<td>−31.45²</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AI (events/h)</td>
<td>0.5 ± 0.6</td>
<td>38.8 ± 25.3</td>
<td>−14.91²</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HI (events/h)</td>
<td>2.5 ± 1.9</td>
<td>21.7 ± 17.2</td>
<td>−11.02²</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LSaO₂ (%)</td>
<td>91.0 ± 2.2</td>
<td>75.4 ± 9.3</td>
<td>15.81²</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ARI</td>
<td>10.5 ± 6.3</td>
<td>46.0 ± 21.0</td>
<td>−15.32²</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sleep stage, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REM (%)</td>
<td>23.9 ± 32.8</td>
<td>15.1 ± 5.6</td>
<td>2.61²</td>
<td>0.010</td>
</tr>
<tr>
<td>N1 (%)</td>
<td>14.4 ± 6.0</td>
<td>29.1 ± 13.4</td>
<td>−9.06²</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N2 (%)</td>
<td>63.7 ± 7.6</td>
<td>54.5 ± 12.9</td>
<td>5.25²</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N3 (%)</td>
<td>2.9 ± 5.2</td>
<td>1.2 ± 3.1</td>
<td>1.94⁵</td>
<td>0.058</td>
</tr>
<tr>
<td>Sleep and wake time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>21.8 ± 23.0</td>
<td>12.5 ± 16.8</td>
<td>2.68²</td>
<td>0.008</td>
</tr>
<tr>
<td>REM latency (min)</td>
<td>108.4 ± 62.6</td>
<td>150.6 ± 88.1</td>
<td>−3.23²</td>
<td>0.002</td>
</tr>
<tr>
<td>SE (%)</td>
<td>82.4 ± 12.3</td>
<td>82.9 ± 9.9</td>
<td>−0.22²</td>
<td>0.826</td>
</tr>
<tr>
<td>TST (min)</td>
<td>417.3 ± 75.7</td>
<td>428.3 ± 81.4</td>
<td>−0.75²</td>
<td>0.455</td>
</tr>
</tbody>
</table>

Note: Data are expressed as mean ± standard deviation.

Abbreviations: OSA, obstructive sleep apnea; AHI, apnea hypopnea index; ARI, arousals per hour; LSaO₂, lowest oxygen saturation; TST, total sleep time; SE, sleep efficiency; REM, rapid eye movement; N1, non-REM (NREM) stage 1; N2, NREM stage 2; N3, NREM stage 3; R, REM stage.
Correlation Between AHI, Relative Spectral Power and Frequency Band Ratios of All the Participants

The correlation between AHI and relative spectral power in total participants is shown in Table 4. AHI was positively correlated with beta power during NREM sleep ($r = 0.229$, $p = 0.006$) and total sleep ($r = 0.204$, $p = 0.015$), and delta power during REM sleep ($r = 0.203$, $p = 0.016$). AHI was negatively correlated with TBR during NREM sleep ($r = −0.324$, $p < 0.001$) and total sleep ($r = −0.312$, $p < 0.001$). AHI was negatively correlated with theta power during REM sleep ($r = −0.237$, $p = 0.005$) and total sleep ($r = −0.175$, $p = 0.038$).

The correlation between arousal index and relative spectral power in total participants is listed in Table 5. Arousal index was positively correlated with theta power and TBR in all participants during NREM ($r = −0.344$, $p < 0.001$), REM ($r = −0.204$, $p = 0.015$) and total sleep stages ($r = −0.338$, $p < 0.001$).

Discussion

Our study first evaluated sleep EEG changes in OSA patients using frequency band ratio, especially TBR, which may facilitate further investigation on the pathophysiological mechanisms of cognitive impairments in OSA patients. Spectral power analysis was performed on sleep EEG derived from PSG recordings of the general population, and the spectral power of severe OSA patients and controls was compared. The results showed that TBR was significantly decreased in
OSA patients during NREM sleep, REM sleep and total sleep. The decreased TBR was caused by both the decreased theta power and the increased beta power. In addition, TBR was negatively correlated with AHI during NREM sleep and total sleep. Higher beta power was found in OSA patients compared to controls (Table 3), and the beta power was positively correlated with AHI and arousal index in all participants during NREM sleep and total sleep (Tables 4 and 5). The higher beta power can be explained by higher background brain activity, which means shallower sleep in OSA patients. It was consistent with the microstructure of sleep in OSA patients who had a significantly increased percentage of N1 sleep.
Consistent with our findings, a previous study found that beta and delta power during NREM sleep was higher in OSA participants than in the simple snoring subjects.\(^9\) Another study investigated the degree of daytime sleepiness and the characteristics of the sleep EEG by examining the macro- and microstructure of sleep among patients with OSA and upper airway resistance syndrome (UARS) and normal controls, and it was found that the OSA patients had significantly higher beta power during NREM sleep and lower delta power during all sleep stages compared to the controls, which was consistent with the outcomes of our study.\(^{25}\) A recent study also confirmed the increasing trend of beta power with the severity of OSA using large-scale data (n = 4493) and controlled the covariates that could affect the spectral sleep EEG.\(^{26}\) However, it was found that the relative beta power was higher during N3 sleep and lower during N2 sleep in the sleep apnea group than in the healthy group, and the change in beta power depended on the sleep stage.\(^{27}\) More specifically, we found a positive correlation between the beta power activity and AHI in NREM sleep and total sleep, which implies that beta power may be linearly correlated with increased background activity and arousals in OSA patients compared with the controls.

The theta power of OSA patients during NREM sleep, REM sleep and total sleep was significantly lower compared with the controls. The decreased theta power can be explained by the attenuation of slow wave sleep EEG which may inversely cause waking EEG slowing.\(^{28}\) The waking EEG slowing has been linked to greater subjectively rated levels of sleepiness and fatigue\(^{29,30}\) and objectively measured lapses in attention and vigilance failure.\(^{31}\) A previous study was performed on older adults with self-reported cognitive decline, and increased theta power in wake-EEG at the baseline was found in participants who presented an objective cognitive decline during 7–9 years of follow-up.\(^{32}\) Consistent with our results, an earlier study found reduced theta activity in NREM sleep predicted increased daytime sleepiness measured by the Multiple Sleep Latency Test (MSLT),\(^{33}\) while greater slow wave activity (SWA) during slow wave sleep (SWS) was related to improved declarative memory, procedural learning and faster reaction.\(^{34}\) However, inconsistent results have also been reported, which showed no significant differences in the theta frequency during NREM and REM sleep between groups.\(^9,25\)

| Table 4 Correlation Analyses Between AHI, Relative Spectral Power and Frequency Band Ratios of All the Participants |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | NREM Sleep      |                | REM Sleep       |                | Total Sleep     |                |
|                | r               | p-value        | r               | p-value        | r               | p-value        |
| Delta (1–4Hz)  | 0.079           | 0.351          | 0.203           | 0.016          | 0.093           | 0.274          |
| Theta (4–8 Hz) | −0.162          | 0.054          | −0.237          | 0.005          | −0.175          | 0.038          |
| Alpha (8–12Hz) | −0.095          | 0.261          | −0.174          | 0.038          | −0.105          | 0.212          |
| Sigma (12–15Hz)| −0.044          | 0.602          | −0.064          | 0.447          | −0.037          | 0.661          |
| Beta (15–20Hz) | 0.229           | 0.006          | −0.020          | 0.809          | 0.204           | 0.015          |
| TAR            | −0.009          | 0.916          | −0.029          | 0.728          | −0.002          | 0.978          |
| TBR            | −0.324          | <0.001         | −0.162          | 0.054          | −0.312          | <0.001         |

Abbreviations: TAR, theta/alpha ratio; TBR, theta/beta ratio.

| Table 5 Correlation Between Arousal Index, Relative Spectral Power and Frequency Band Ratios of All the Participants |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                | NREM Sleep      |                | REM Sleep       |                | Total Sleep     |                |
|                | r               | p-value        | r               | p-value        | r               | p-value        |
| Delta (1–4Hz)  | 0.147           | 0.080          | 0.289           | 0.000          | 0.162           | 0.054          |
| Theta (4–8 Hz) | −0.241          | 0.004          | −0.336          | 0.000          | −0.255          | 0.002          |
| Alpha (8–12Hz) | −0.166          | 0.049          | −0.248          | 0.003          | −0.179          | 0.033          |
| Sigma (12–15Hz)| −0.055          | 0.514          | −0.084          | 0.318          | −0.049          | 0.562          |
| Beta (15–20Hz) | 0.234           | 0.005          | −0.040          | 0.634          | 0.207           | 0.014          |
| TAR            | 0.008           | 0.924          | −0.020          | 0.817          | 0.015           | 0.860          |
| TBR            | −0.344          | <0.001         | −0.204          | 0.015          | −0.338          | <0.001         |

Abbreviations: TAR, theta/alpha ratio; TBR, theta/beta ratio.
Theta waves are linked to subcortical brain regions involved in affective processes, whereas beta activity that is argued to reside at the thalamo-cortical and cortico-cortical level is associated with emotional and cognitive control processes and arousal during sleep.\textsuperscript{19,35} TBR is argued to reflect cortico-subcortical interactions. Accumulating evidence indicates that TBR might be a promising electrophysiological marker for cognitive control in healthy adults\textsuperscript{12–14} and children with ADHD. Increased theta/beta ratio in awake EEG has been observed in children with ADHD.\textsuperscript{16} In the current study, both lower theta power and higher beta power were observed in OSA patients, which resulted in significantly decreased TBR. The finding that the effect sizes of TBR were over 0.8 for both NREM sleep and total sleep suggests that the differences were clinically meaningful with large effect. Therefore, TBR may be a more stable EEG-biomarker of OSA patients, which may accurately and reliably identify the disease/non-disease states of OSA even to evaluate the changes of EEG after treatment in the future.

Our study showed different patterns of spectral power during NREM and REM sleep. Significantly increased delta power of OSA patients was found only during REM sleep. Delta band power activity was shown to be positively correlated with AHI and ArI in REM sleep. That is, patients with higher EEG slowing are more prone to arousals, resulting in sleep fragmentation. This is supported by previous studies, which demonstrated an increase in delta power and a decrease in theta power in the severe OSA group compared to primary snoring and mild-moderate groups.\textsuperscript{10} One study including 76 patients with OSA found that higher delta power in REM sleep and higher beta power in NREM sleep were predictors of worse steering deviation on a 30-minute driving simulator task.\textsuperscript{36} Inconsistent findings have also been reported, that is, higher delta activity during NREM sleep in OSA patients than in controls\textsuperscript{37} or simple snoring participants.\textsuperscript{9} The finding of increased delta power in REM sleep might be interpreted that REM sleep was interrupted by arousal and sleep spindles, which are relatively faster than REM sleep.

The major limitation of our research is the lack of cognitive evaluation. Therefore, the causal relationship between TBR and cognitive decline caused by OSA cannot be determined. It is suggested that cognitive related evaluation should be considered in future research. The main limitations of this study also included small and unmatched sample size between OSA patients and controls due to the clinical characteristics of the disease. Moreover, we only included middle-aged severe OSA patients; since earlier studies have shown that the macrostructural and microstructural features have age-related changes, we chose the middle-aged group which is mostly affected by OSA. Meanwhile, it is speculated that brain dysfunction is susceptible to the severity of OSA, so we only included patients with severe OSA. Our findings remain to be further verified by studies with a larger sample size and OSA patients of different severity.

**Conclusion**

In summary, the major finding of the present study is that TBR was significantly decreased in severe OSA patients compared with controls, which is attributed to both the general increase in beta power and the decrease in theta power. Meantime, TBR was negatively correlated with AHI and arousal index. TBR may be a more stable EEG-biomarker of OSA patients, which may accurately and reliably identify the disease/non-disease states of OSA even to evaluate the changes of EEG after treatment in the future. However, the stability of TBR, the correlation between TBR and subjective assessment of cognitive function and the changes before and after therapy of OSA remain to be investigated in the future.

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**Disclosure**

The authors report no conflicts of interest in this work.
References