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ORIGINAL RESEARCH

Phase-Amplitude Coupling in Theta and Beta Bands: A Potential Electrophysiological Marker for Obstructive Sleep Apnea

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Background: Phase-amplitude coupling (PAC) between the phase of low-frequency signals and the amplitude of high-frequency activities plays many physiological roles and is involved in the pathological processed of various neurological disorders. However, how low-frequency and high-frequency neural oscillations or information synchronization activities change under chronic central hypoxia in OSA patients and whether these changes are closely associated with OSA remains largely unexplored. This study arm to elucidate the long-term consequences of OSA-related oxygen deprivation on central nervous system function.

Methods: : We screened 521 patients who were clinically suspected of having OSA at our neurology and sleep centers. Through polysomnography (PSG) and other clinical examinations, 103 patients were ultimately included in the study and classified into mild, moderate, and severe OSA groups based on the severity of hypoxia determined by PSG. We utilized the phase-amplitude coupling (PAC) method to analyze the modulation index (MI) trends between different frequency bands during NREM (N1/N2/N3), REM, and wakefulness stages in OSA patients with varying severity levels. We also examined the correlation between the MI index and OSA hypoxia indices.

Results: Apart from reduced N2 sleep duration and increased microarousal index, the sleep architecture remained largely unchanged among OSA patients with varying severity levels. Compared to the mild OSA group, patients with moderate and severe OSA exhibited higher MI values of PAC in the low-frequency theta phase and high-frequency beta amplitude in the frontal and occipital regions during N1 sleep and wakefulness. No significant differences in the MI of phase-amplitude coupling were observed during N2/3 and REM sleep. Moreover, the MI of phase-amplitude coupling in theta and beta bands positively correlated with hypoxia-related indices, including the apnea-hypopnea index (AHI) and oxygenation desaturation index (ODI), and the percentage of oxygen saturation below 90% (SaO2<90%).

Conclusion: OSA patients demonstrated increased MI values of theta phase and beta amplitude in the frontal and occipital regions during N1 sleep and wakefulness. This suggests that cortical coupling is prevalent and exhibits sleep-stage-specific patterns in OSA. Theta-beta PAC during N1 and wakefulness was positively correlated with hypoxia-related indices, suggesting a potential relationship between these neural oscillations and OSA severity. The present study provides new insights into the relationship between neural oscillations and respiratory hypoxia in OSA patients.

Keywords: phase-amplitude coupling, PAC, modulation index, MI, obstructive sleep apnea, polysomnography, EEG

Introduction

Obstructive sleep apnea (OSA) a prevalent sleep-related respiratory disorder, affects a significant portion of the adult population.[1,2] Characterized by recurrent upper airway obstruction (apnea) during sleep, OSA lead to sleep fragmentation,[3,4]

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intermittent hypoxia, snoring, and excessive daytime somnolence.[5] Long-term chronic hypoxia associated with OSA can induce central nervous system dysfunction, manifesting as cognitive impairment and behavioral abnormalities.[6–9] Increasing evidence implicates OSA in the etiology of neuropsychiatric disorders and cardiovascular disease, underscoring its far-reaching health implications.[10–13] Sleep electroencephalography (EEG) has been utilized as a valuable tool for monitoring cerebral electrical activity in OSA patients,[14–16] Our preliminary study has identified abnormal sleep EEG spectral patterns in these individuals, characterized by reduced power in low-frequency theta and alpha bands, and high-frequency beta oscillations, correlating with indicators of chronic hypoxia.[14] These results shed light on the effects of OSA on cortical activity from an electrophysiological perspective. However, EEG researches of OSA have predominantly focused on spectral analysis, offering scant insights into the modulation of global brain network dynamics. The modulation of neural oscillations across high and low frequency EEG bands in OSA patients and their potential as electrophysiological markers of OSA severity, remains to be elucidated.

This study investigates the characteristics of neural oscillatory coupling in the frontal and occipital cortices of OSA patients across severity levels. We hypothesize that phase-amplitude coupling (PAC) values will vary among OSA patients, potentially correlating with disease severity and chronic hypoxia. By analyzing the modulation index of various frequency combinations (1–45 Hz) using three distinct calculation methods, we aim to elucidate the long-term consequences of OSA-related oxygen deprivation on central nervous system function.

Sleep is characterized by dynamic fluctuations in information exchange and neural oscillation connectivity across distinct cerebral regions. These oscillations exhibit intricate mutual influences and regulatory functions. Cross-frequency coupling, particularly phase-amplitude coupling (PAC),[17] exemplifies this phenomenon, reflecting the synchronization between low-frequency phases and high-frequency amplitudes. This coupling is intimately linked to neural plasticity, cognitive learning, memory formation, and sensory mechanisms.[18–20] Research has elucidated that the modulation index (MI) provides a more robust assessment of signal-to-noise ratio, amplitude independence, multimodal sensitivity, and modulation width.[21] Sleep EEG analyses in healthy adults have demonstrated that PAC exhibits stage-dependent flow directions, with low-frequency delta-theta/alpha bands PAC progressively intensifies concomitant with deepening of sleep.[22] Consequently, PAC is regarded as an effective biomarker for the modulation of low-frequency activity and the synchronization within high-frequency bands. Exploring neurophysiological connectivity patterns and oscillations dynamics could enhance our understanding of the pathophysiological mechanisms underlying OSA.[23]

Cross-frequency coupling may elucidate the network patterns of different frequency bands in OSA patients. Studies have shown that sleep disturbances may affect cortical information transmission based on cross-frequency PAC.[24] EEG studies have identified distinct characteristics of low and high-frequency oscillations in OSA, indicating engagement of cortical activity in chronic hypoxia. PAC features have shown remarkable sensitivity to various sleep-related disorders.[25] Additionally, the combination of PAC with Random Forest classification models has demonstrated efficacy in distinguishing between seven sleep disorders.[21] In OSA, reduced MI values for theta-gamma oscillations have been observed in the somatosensory-motor cortex across all sleep stages, while delta-alpha coupling demonstrates opposite changes during NREM and REM periods.[26]

Our study aims to investigate the characteristics of neural oscillatory coupling in the frontal and occipital cortices of OSA patients with different severity levels, and to determine whether the inter-frequency coupling of neural oscillatory could serve as a sensitive indicator of OSA severity. We hypothesized that PAC values will vary with OSA severity, potentially reflecting a correlation with OSA severity and chronic hypoxia. By analyzing the modulation index of frequency combinations from 1 to 45 Hz using three distinct calculation methods (klmi, mvlmi, and plv), we seek to uncover novel electrophysiological biomarkers for OSA. This investigation promises to enhance our understanding of OSA's underlying pathophysiology and potentially revolutionize the assessment of disease severity and progression. By exploring the intricate relationships between neural oscillations and chronic hypoxia, we aim to pave the way for more targeted interventions and improved patient outcomes in OSA management.

Materials and Methods

Study Population

This retrospective study was conducted at the Department of Neurology at the First Affiliated Hospital of Zhengzhou University in China. It included 521 patients with snoring symptoms and clinical suspicion of OSA from 2020 to 2023.

To ensure the accuracy of the study, certain exclusion criteria were applied. Patients with other types of sleep disorders, such as central sleep apnea, rapid eye movement sleep behavior disorder, restless legs syndrome, and periodic limb movement disorder were excluded. Additionally, individuals who had taken medications known to affect sleep status (eg, hypnotics, benzodiazepines) within the past month were also excluded. Patients with significant artefacts in their EEG signals, as well as those with severe pulmonary, renal, hepatic, and cerebral disorders were excluded as well (Figure 1). Finally, clinical data and PSG studies of 103 subjects were selected for analysis. We considered apnea-hypopnea index (AHI) and oxygenation desaturation index (ODI) and the percentage of oxygen saturation less than 90% (SaO2<90%) in order to evaluate the severity of nighttime hypoxia. The subjects were divided into three groups based on previous study: mild OSA group (5 ≤ AHI < 15 events/hour, N=27), moderate OSA group (15 ≤ AH I< 30 events/hour, N=30), and severe OSA group (30≤AHI events/hour, N=46) (Figure 1 and Table 1).[14] The study was conducted in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University, and the requirement for informed consent was waived (Ethics Approval No. 2022 [101]). We pledge to strictly adhere to patient data confidentiality and take all necessary measures to protect patient privacy.

All Night Polysomnography

Sleep apnoea was confirmed by nocturnal polysomnography (PSG, Embla 4500S, Ambulatory Monitoring Inc., Ardsley, NY, U.S.A).[27] A total of 6 EEG signals (F3-M2, F4-M1, C1-M2, C2-M1, O1-M2, and O2-M1), 2 electro-ocular signals (E1-M2, E2-M2), and chin EMG (EMG1-EMG2, EMG EMG3), electrocardiogram (ECG), respiration (nasal pressure, airflow), oxygen saturation (SpO2), abdominal-thoracic movements and leg movements were recorded.[28] Due to limitations in the collection equipment and techniques, the central channel signals (C1/C2) were not included in the analysis. Sleep stages and respiratory events were analyzed based on the guidelines recommended by the AASM scoring criteria.[29] Sleep stages were categorized as non-rapid eye movement (NREM) sleep, which includes stages N1, N2, and N3, rapid eye movement (REM) sleep and wakefulness. Sleep-related parameters such as including bedtime, total sleep time (TST), sleep latency (SL), sleep efficiency (SE), wakefulness after sleep onset (WASO), and the ratio of each sleep stage (N1/TST, N2/TST, and N3/TST) to the total sleep time were calculated and reported in the PSG study (Table 1).

Data Analysis (Pre-Processing)

We recorded the scalp EEG signals of the sleep participants using non-invasive electrodes, as described in the overnight PSG method. EEG signals were recorded at a sampling rate of at 200 Hz and stored in EDF format. We selected EEG data from the first two sleep cycles for analysis by reviewing the entire night's PSG data. Initially, we preprocessed 3–12 minutes of raw data from each stage of the sleep cycle (NREM, REM, and wakefulness). The EEG signals were preprocessed using MATLAB software (MATLAB 2013a). The raw signals were subjected to a bandpass filter of 0.5–45.0 Hz using the EEGLab software (eeglab14_0_0b Yueying Technology). The data underwent preprocessing through artifact removal, eliminating data with an amplitude of ± 80 mV, and utilized Independent Component Analysis (ICA) to remove interference from eye movements and electromyographic noise.[11,30] Finally, we chose 3 minutes of the preprocessed data from four channels (F3-M2, F4-M1, O1-M2 and O2-M1) for further analysis.

Phase-Amplitude Coupling Analysis

We analyzed modulation indices (MI) for various frequencies ranging from 1 to 45 Hz using three different computation methods (the Kullback–Leibler based modulation index, klmi; the mean vector length modulation index, mvlmi; the Phase-Locking Value, plv) with the FieldTrip toolbox. In our initial step, we utilized the EEGfilt function within EEGLAB to extract low- and high-frequency signals. Subsequently, by employing a Hilbert transform with a 2 Hz increment, we acquired the instantaneous amplitudes of signals in the high-frequency range (7 to 45 Hz) and the instantaneous phases of signals in the low-frequency range (1 to 29 Hz). The phase angles of the low-frequency signals were segmented into eighteen bins, each spanning 20 degrees from -π to π, and the corresponding mean amplitudes of the high-frequency signals for each bin were calculated. To normalize the mean amplitude within each bin, we divided the value of each bin by the sum of the values across all 18 bins, yielding a phase-amplitude distribution. MI values were

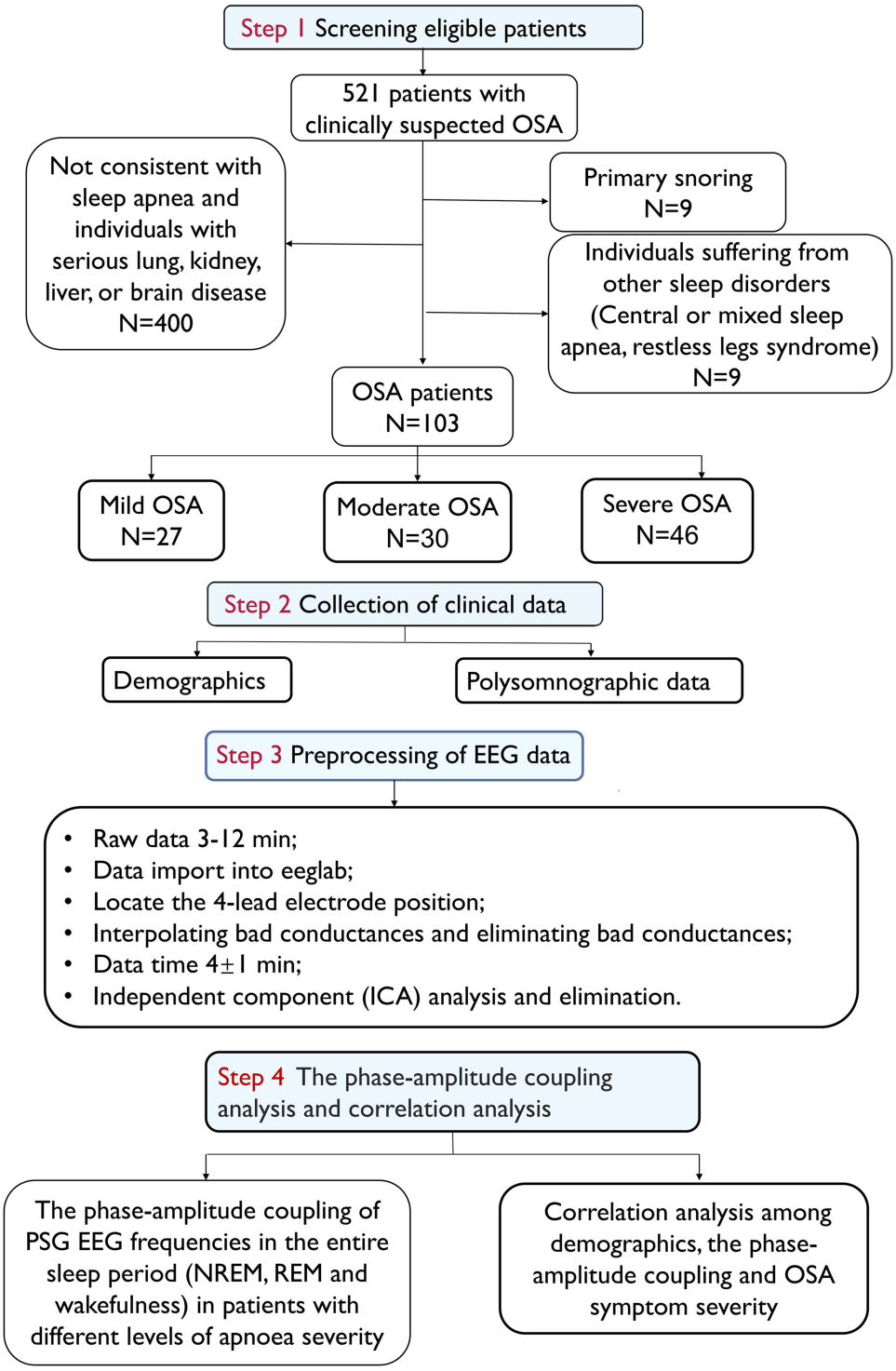

Figure 1 Flow chart of patient screening and grouping, clinical data collection, sleep EEG processing and data analysis.

calculated for each frequency pair.[31] The MI values, ranging from 0 to 1,[32] with an MI of 1 indicating maximal phase-amplitude coupling, and an MI of 0 indicating no coupling. To visualize represent our findings, we plotted co-modulation plots of MI values for each channel across different sleep stages in OSA patients. In this study, we performed statistical analysis on the MI values for the low-frequency theta (5–7 Hz) and high-frequency beta (25–29 Hz) band of interest, and

Table 1 Characteristics of the Population (N = 103) Categorized by OSA Severity

Parameter	Mild OSA (N=27)	Moderate OSA (N=30)	Severe OSA (N=46)	Statistics	
Demographics					
Age, years	53.67±12.67	55.93±13.61	55.93±10.94	F=0.3431	P=0.7104
Sex, male	14 (51.85%)	24 (80.00%)	40 (86.96%)	F=6.486	P=0.0022**
BMI, kg/m2	25.85±3.835	25.89±3.355	29.55±6.515	F=5.508	P=0.0057**
Polysomnographic data					
AHI, /hr	8.459±2.569	20.66±4.319	47.81±14.73	F=141.9	P<0.0001****
AHI during NREM, /hr	7.733±3.218	20.10±5.078	48.20±15.84	F=128.0	P<0.0001****
AHI during REM, /hr	14.39±11.41	21.42±16.06	44.98±18.38	F=36.67	P<0.0001****
AHE	53.48±22.71	126.4±46.55	306.2±163.8	F= 48.52	P<0.0001****
AHE during NREM	41.7±21.61	102.1±40.16	258.0±140.8	F=48.26	P<0.0001****
AHE during REM	11.78±9.677	24.33±19.89	48.22±35.46	F=17.66	P<0.0001****
MAI, /hr	2.778±2.423	3.800±2.618	10.41±11.56	F= 10.19	P<0.0001****
MAI during NREM, /hr	2.333±2.075	3.267±2.348	8.826±9.987	F= 9.760	P<0.0001****
MAI during REM, /hr	0.4444±0.5774	0.5000±0.6297	1.500±2.074	F= 6.285	P=0.0027**
ODI, /hr	6.133±3.617	16.03±8.393	31.59±15.99	F=42.57	P<0.0001****
SaO2<90%, %	6.107±12.74	9.097±10.71	25.67±18.38	F=18.38	P<0.0001****
Time in bed, min	542.2±57.81	515.7±73.86	545.7±66.72	F=1.996	P=0.1413
Total sleep time, min	376.4±87.91	364.6±104.6	371.0±107.9	F=0.09513	P=0.9093
Sleep latency, min	35.06±31.91	26.89±30.32	31.61±39.05	F=0.3964	P=0.6738
REM sleep latency, min	126.9±116.5	97.58±75.65	98.60±72.77	F=1.087	P=0.3413
Sleep efficiency, %	74.51±15.89	74.43±17.49	72.21±17.08	F=0.2276	P=0.7968
WASO, min	130.8±84.85	124.2±83.93	143.1±93.35	F=0.4444	P=0.6425
NREM 1%	22.28±9.395	23.19±15.38	25.13±11.24	F=0.5234	P=0.5941
NREM 2%	37.49±10.42	35.83±11.39	30.10±11.67	F=4.399	P=0.0148*
NREM 3%	25.76±8.881	24.82±13.50	28.33±15.09	F=0.7142	P=0.4920
REM %	14.48±6.239	16.14±7.551	17.30±7.357	F=1.326	P=0.2703

Notes: Data are means ± standard deviations; [a]indicates the percentage value for the sample. The P values represent the difference between the mild OSA group and the severe OSA group. *p-value significant at < 0.05; **p-value significant at < 0.001; ****p-value significant at < 0.0001.

Abbreviations: N, sample size; BMI, body mass index; AHI, apnea-hypopnea index; NREM, non-rapid eye movement; REM, rapid eye movement, AHE, apnoea and hypopnoea event; MAI, microarousal index; /hr, event per hour; ODI, oxygenation desaturation index; SaO2<90%, the percentage of oxygen saturation less than 90%; WASO, wake time after sleep onset; NREM 1%, percentage of nonrapid eye movement stage 1 sleep time; NREM 2%, percentage of nonrapid eye movement stage 2 sleep time; NREM 3%, percentage of nonrapid eye movement stage 3 sleep time; REM %, percentage of rapid eye movement sleep time.

further analyzed the correlation between theta-beta MI values and hypoxia indices in PSG metrics (see flowchart in Figure 1, Step 4).

Statistical Analysis

GraphPad Prism (version 8.3.0) and SPSS (version 26.0) software were used for statistical analysis and plotting. Data were expressed as mean ± standard deviation, unless otherwise as number (percentages in parentheses). MI statistical variables of the three OSA groups were compared using one-way ANOVA. Correlation analyses were performed using Pearson's two-tailed *t*-test. A significance level of $p < 0.05$ was considered statistically significant.

Results

Demographic and PSG Characteristics of OSA Patients

An initial cohort of 521 patients with clinical suspicion of OSA was identified. Ultimately, 103 patients who were clinically diagnosed with OSA were included in the study. For details of the selection process, please refer to Figure 1. The demographic and PSG characteristics of the three severity groups of OSA were summarized in Table 1. The median age of the patients was 55 years. In terms of demographics, we found a significant difference in body mass index (BMI)

between the severe OSA group and the other two groups (F (2,81) = 5.508, P=0.0057), which is consistent with previous studies. For PSG-related indices, patients with severe OSA exhibited increased apnea-hypopnea index AHI during both NREM sleep (F (2,100) = 128.0, P<0.0001) and REM sleep (F (2,100) = 36.67, P<0.0001). Moreover, apnea and hypoventilation during NREM (F (2,100) = 48.26, P<0.0001) and REM sleep (F (2,100) =17.66, P<0.0001), micro-arousal indices during NREM (F (2,100) = 9.760, P<0.0001) and REM sleep (F (2,100) =6.285, P=0.0027), ODI (F (2,100) = 42.57, P<0.0001) and Sa02<90% (F (2,100) = 18.38, P<0.0001) were significantly higher in patients with severe OSA (Table 1). However, parameters such as bedtime, total sleep time, REM sleep latency, sleep efficiency and wake after sleep onset (WASO) did not differ significantly among the three groups (Table 1). Additionally, except for a decrease in N2 sleep time in severe OSA patients (F (2,100) = 4.399, P = 0.0148), sleep time in other stages did not change.

Phase-Amplitude Coupling Analysis

The results of modulation index (MI) analysis for frequencies ranging from 1 to 45 Hz using three different computational methods (klmi, mvlmi, and plv) were found to be similar. In this study, we present the results obtained using klmi. By analyzing the modulation index of phase at 1–29 Hz and amplitude at 7–45 Hz during each period in the frontal and occipital lobes, it was found that compared to mild OSA patients, moderate and severe OSA patients showed a trend towards higher of MI in the low-frequency (5–7Hz) and high-frequency (25–29Hz) in all sleep periods (Figure 2–4). Figure 2 shown the variations of PAC-MI for the F3/F4 channels across the mild OSA group, moderate OSA group, and severe OSA group during the N1 (Figure 2A), N2 (Figure 2B), N3 (Figure 2C) sleep stages. The variations of PAC-MI for the O1/O3 channels across the N1-N3 stages were shown in Figure 3. Figure 4 illustrates the increase in PAC-MI for the F3/F4 and O1/O2 channels in OSA patients between the REM and wakefulness states. The MI values for the F3/F4 and O2 channels demonstrate a statistically significant increase only in the N1 (F3: F(2, 97) =2.131, P=0.028; F4: F(2, 97)=4.437, P=0.022) and wakefulness periods (F3: F(2, 97)=1.073, P=0.467; F4: F(2, 97)=3.633, P=0.0470; O2: F(2, 99) =3.110, P=0.029; F(2,99) =3.521, P=0.035), as shown in Figure 5.

Correlation Analysis

We further analyzed the correlation between the theta-beta bands MI values during N1 and wakefulness periods and clinical and PSG indicators (Figure 6). Statistical analysis revealed no correlation between gender and MI values. BMI showed a positive correlation with the N1 sleep of F4 channel (r=0.514 P<0.001), the wake sleep of F4 channel (r=0.453 P<0.001) and the wakefulness period of O2 channel (r=0.346, P=0.001). The AHI exhibited a positive correlation with MI value during N1 sleep in the F4 channel (r=0.230, P=0.022), wake period in the F4 channel (r=0.249, P=0.013) and wakefulness in the O2 channel (r=0.235, P=0.019), indicating a relationship between PAC and the severity of sleep-disordered breathing, with higher PAC-MI values associated with more severe conditions. ODI was positively correlated with MI during N1 sleep in the F3 channel (r=0.216, P=0.031), while SaO2<90% was positively correlated with MI values during wake period in the O2 channel (r=0.222, P=0.025), suggesting that PAC could reflect the degree of chronic hypoxia in OSA patients. We categorized the three groups based on AHI while focusing on the correlation between AHI and PAC-MI. The results showed that there was a positive correlation between the MI value of F3 channel and wakefulness only in severe OSA patients (r=0.321, P=0.031), and there was no statistical significance in other analyses. The correlation analysis was shown as individual scatter plots in supplementary Figure 1.

Discussion

Our current understanding of the brain oscillation dynamics associated with Obstructive Sleep Apnea (OSA) is limited and does not provide a comprehensive perspective on this phenomenon. Cortical abnormalities, such as reduced theta and beta power, have been consistently reported in association with OSA. Given that the phase of lower frequencies governs the amplitude of higher frequencies in neural oscillation, and considering the observed abnormal activities in the amplitude of certain frequency bands, we conducted a study on the coupling between the phase and amplitude of different frequency bands in instances where abnormal phase synchrony is associated with Obstructive Sleep Apnea (OSA). Our study found that patients with moderate to severe OSA exhibited an increasing trend in the modulation index (MI) of low-frequency theta phase and high-frequency beta

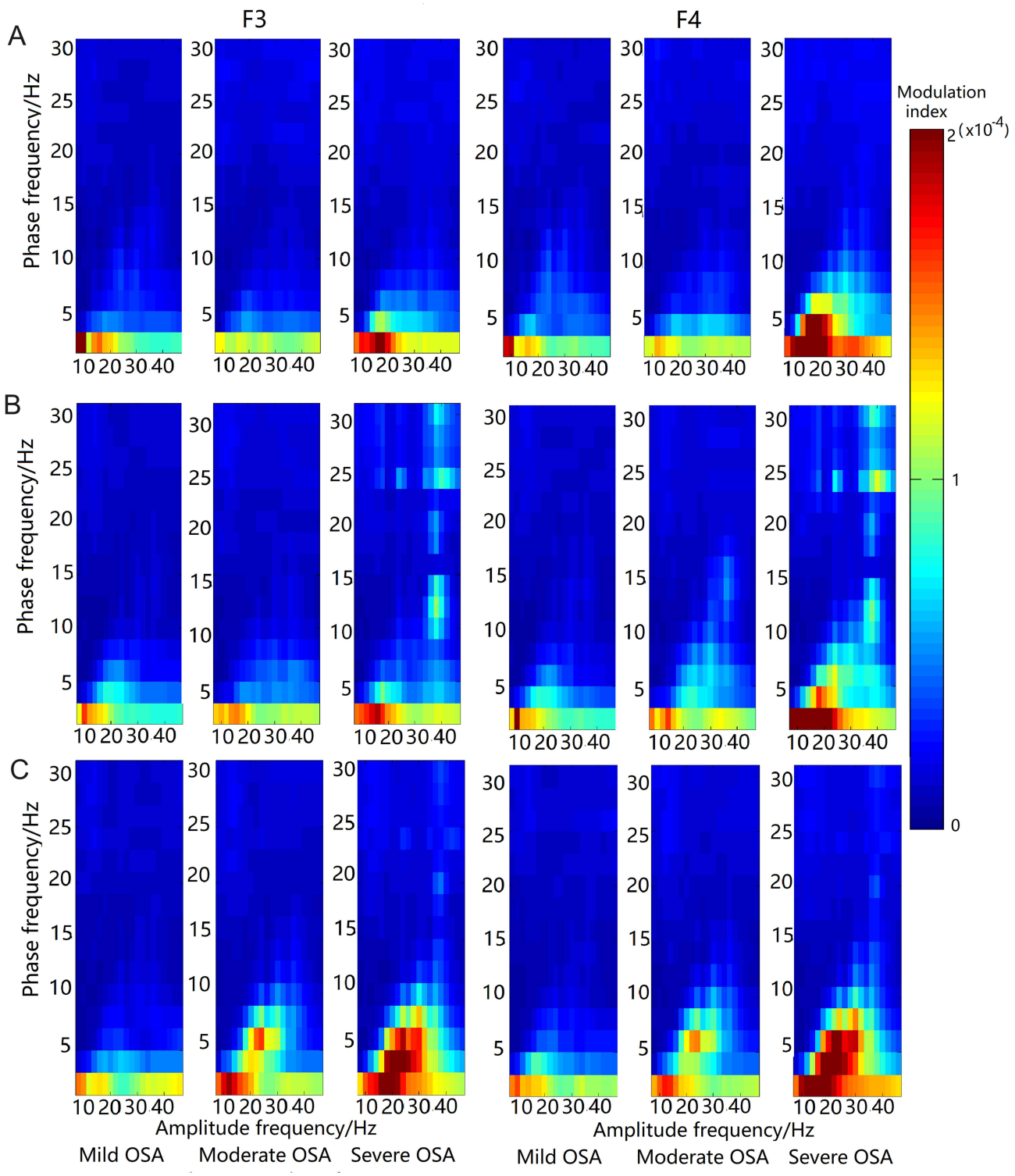

Figure 2 Comodulograms of signals with PAC-MI values in the frontal cortex in OSA patients during the NREM sleep. The modulation index (MI) of amplitudes in the high-frequency range (7–45 Hz) and the phases of signals in the low-frequency range (1–29 Hz) of F3/F4 channels across the mild OSA, moderate OSA, and severe OSA groups during NREM stages N1 (**A**), N2 (**B**), and N3 (**C**). The PAC-MI of the low-frequency (5–7 Hz) and high-frequency (25–29 Hz) was significantly increase in the N1 stage.

amplitude in the frontal and occipital regions during N1 and wakefulness periods, in comparison to patients with mild OSA. The elevated phase-amplitude coupling and OSA-related hypoxia indicators were positively correlated, suggesting that the PAC value may be one of the electrophysiological indicators reflecting the severity of OSA and chronic hypoxia.

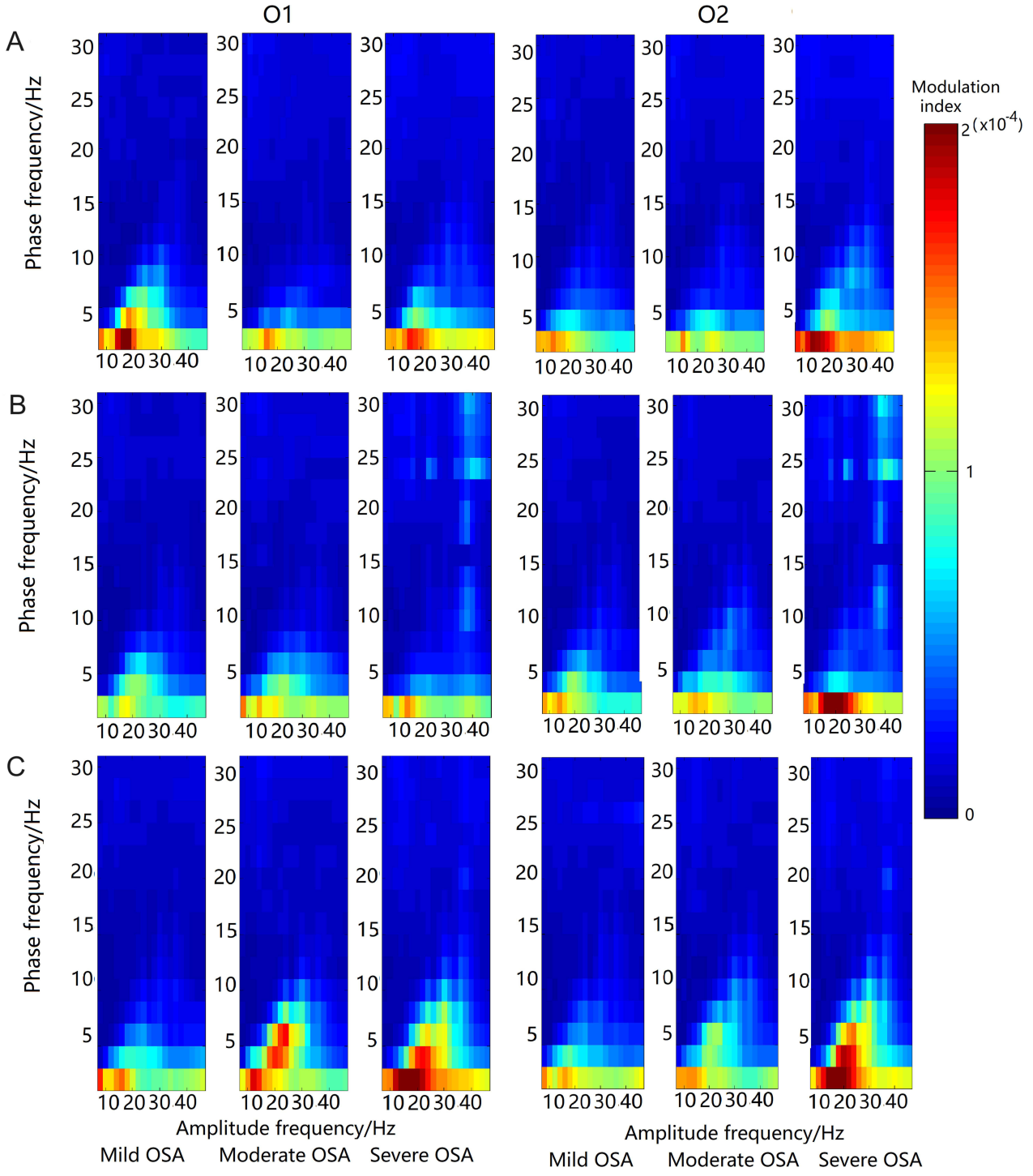

Figure 3 Comodulograms of signals with PAC-MI values in the occipital cortex in OSA patients during the NREM. The modulation index (MI) of amplitudes in the high-frequency range (7–45 Hz) and the phases of signals in the low-frequency range (1–29 Hz) of O1/O2 channels across the mild OSA, moderate OSA, and severe OSA groups during NREM stages N1 (**A**), N2 (**B**), and N3 (**C**). The PAC-MI of the low-frequency (5–7 Hz) and high-frequency (25–29 Hz) was also significantly increase in the N1 stage.

EEG-PAC and OSA

PAC is a neuronal oscillation phenomenon that reflects interactions between neural oscillations of different frequencies. It is considered a crucial mechanism for brain information processing and integration, and can be used for diagnosing and stratifying the severity of brain disorders and neurodegenerative diseases.[33,34] OSA is a common sleep disorder that can lead to intermittent hypoxia and sleep fragmentation, affecting brain function.[6–9] Studies have shown that children exhibit

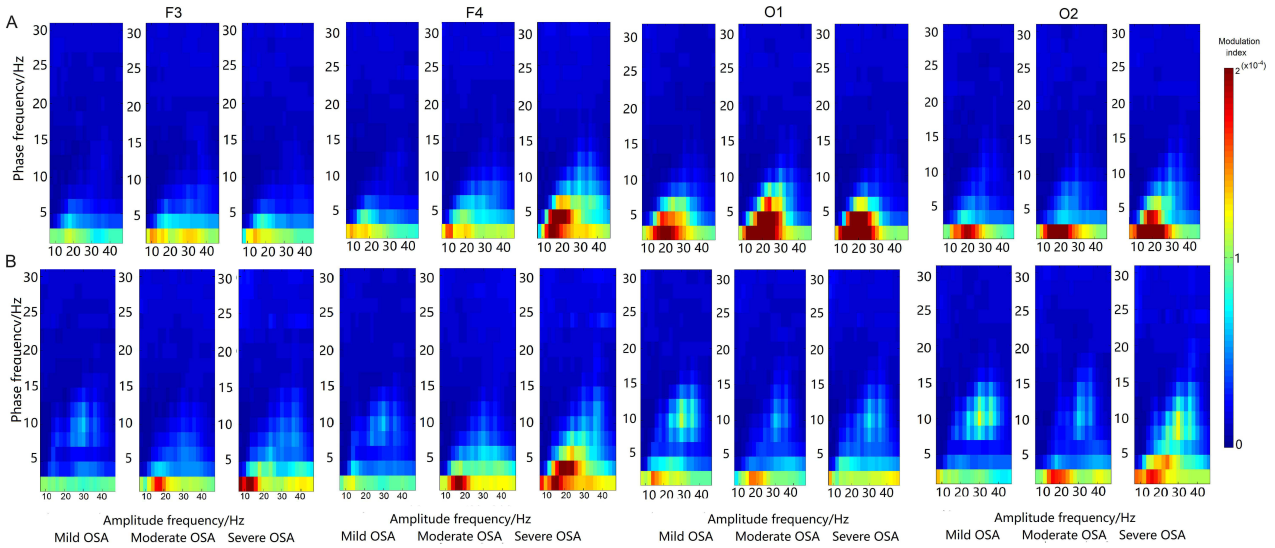

Figure 4 Comodulograms of signals with PAC-MI values in the frontal and occipital cortex in OSA patients during the REM sleep and wakefulness. The modulation index (MI) of high-frequency amplitudes (7–45 Hz) and low-frequency phases (1–29 Hz) for the F3/F4 and O1/O2 channels across the mild OSA, moderate OSA, and severe OSA groups showed no statistically significant differences during REM sleep (**A**); however, it increased significantly during wakefulness (**B**).

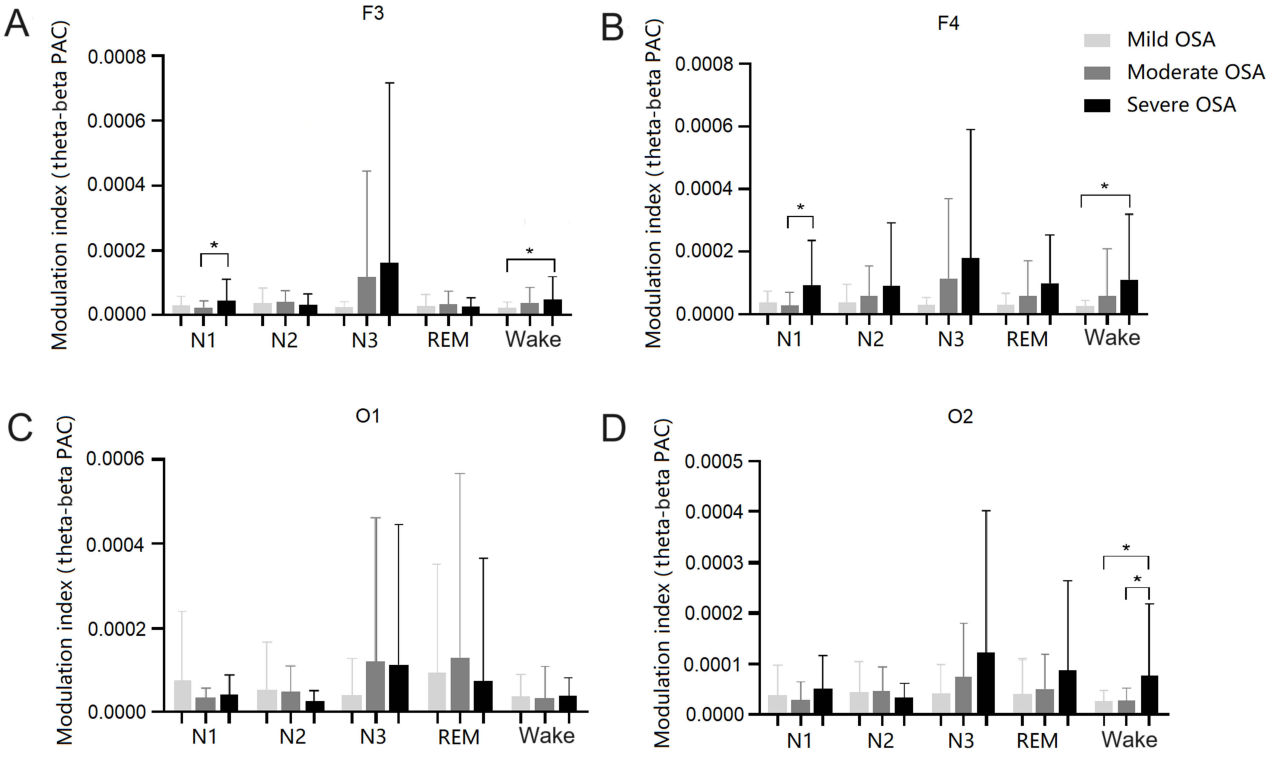

Figure 5 Histogram of the theta-beta PAC-MI in the whole sleep stages in OSA patients. (**A** and **B**) Comprise with mild OSA and moderate OSA group, the theta-beta PAC-MI of F3/F4 channel in the severe OSA group was significantly increase in NRME N1 and wakefulness. (**C**) The theta-beta PAC-MI of O1 channel in the whole sleep states had no statistically significant differences in the three OSA groups. (**D**) In O2 channel, the theta-beta PAC-MI in the severe OSA group was significantly increase only in the wakefulness period. Star symbols represent statistical significance levels: * represents $p < 0.05$, no stars represent $p > 0.05$.

different patterns of slow-wave modulation of high-frequency neural activity across sleep stages. Piantoni et al (2013) found that OSA patients had reduced θ-γ coupling strength during slow-wave sleep.[35] Erlan et al discovered that white matter damage is associated with patterns of high neuronal synchronicity during sleep stages, suggesting a link between white matter damage and chronic fatigue symptoms.[36] J Rajeswari et al's study on brain functional connectivity in OSA

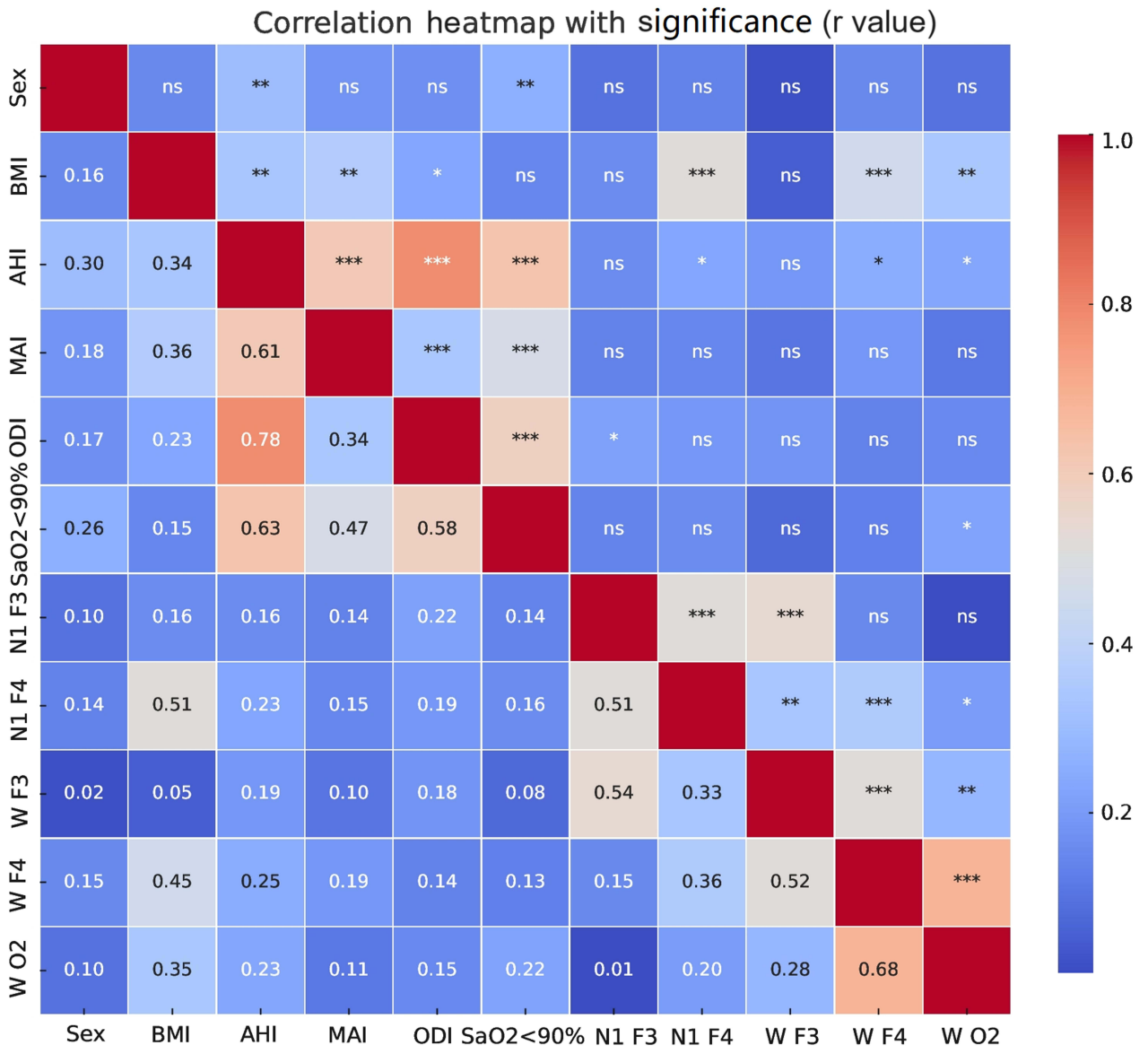

Figure 6 Matrix of Pearson's correlation coefficients among demographics, PAC-MI, OSA symptom severity. BMI showed a positive correlation with the N1 sleep and wakefulness of F4/O2 channel. The AHI exhibited a positive correlation with MI value during N1 sleep and wakefulness of F4/O2 channel. ODI was positively correlated with MI during N1 sleep in the F3 channel, while SaO2<90% was positively correlated with MI values during wake period in the O2 channel. A color-coded correlation scale is presented on the right of the plot. Based upon the scale, blue ones stand for lower correlations and red ellipses stand for higher correlations, ns illustrate insignificant correlations of a given variable with itself. Star symbols represent statistical significance levels: *** represents $p < 0.001$, ** represents $p < 0.01$, * represents $p < 0.05$, no stars represent $p > 0.05$. MAI: microarousal index.

patients revealed that the low-frequency delta band is closely related to OSA. The nodes and edges of the delta band highlighted the connection between the brain and OSA subjects, distinguishing OSA from healthy subjects.[37] Recent research by Silverstein BH et al shows that sedative drugs, while reducing sleep quality and increasing wake time, also decrease the high-frequency gamma-weighted phase-lag index associated with wakefulness.[38] Haralampos et al proposed that OSA patients exhibit significantly reduced sleep stage-specific PAC in sensorimotor areas, providing an objective marker for quantifying daytime sleepiness and respiratory distress in OSA.[25] More longitudinal studies are needed to understand how OSA affects PAC over time and whether changes in PAC can predict long-term outcomes in OSA. Further exploration of the relationship between PAC and other sleep parameters (such as sleep staging and micro-arousals) may provide new insights into the pathophysiological mechanisms of OSA.

PAC-MI Value of Low Frequency Theta Phase and High Frequency Beta in Phase N1

Theta waves and beta waves are two primary waveforms observed in EEG, with the highest power observed in the frontal lobe. Theta waves are commonly associated with states of relaxation and meditation, whereas beta waves are linked to wakefulness, focus, and cognitive activity.[39] Both theta and beta power have been found to be associated with OSA.[40,41] However, Relatively limited attention has been given to theta-beta PAC or PAC in general in patients with OSA. PAC is considered as a fundamental neurological process that promotes synchronization between local and global networks in the brain.[42] It also connects and integrates activity across different frequency bands.[43–45]

Our study revealed that in the N1 phase of NREM sleep, which marks the initial transition from wakefulness to sleep, there was a significant increase in PAC of theta and beta frequencies in the frontal lobe region of moderate and severe OSA groups, as compared to the mild OSA group. This suggests augmented synchronization of neural oscillations within the theta and beta frequency ranges, potentially indicating a disruption in the transitional state between relaxation and wakefulness in the brains of OSA patients.[46] Consequently, this situation could lead to an increased occurrence of wakefulness periods during sleep, adversely affecting sleep quality. Moreover, the observed enhancement in synchronization may potentially indicate adaptive changes within the brains of individuals with OSA as they cope with sleep disruptions and hypoxemia-induced stress. Importantly, we also found that enhancement in theta-beta PAC was prominent not only in the frontal lobe but also in the occipital lobe, and this was closely associated with hypoxia indicators. This suggests that chronic nocturnal hypoxia may intensify modulation of neural oscillations in both the frontal and occipital cortices, aligning with findings from previous studies.[47,48] These findings emphasize the complex interplay between OSA-related physiological challenges and neurological adaptations. Further research is essential to validate these findings. To ascertain the precise significance and underlying mechanisms of this synchronization enhancement, a larger sample size and more comprehensive analysis are warranted. Additionally, it is crucial to explore the potential impact of enhancement synchronization on the daily functioning and quality of life of individuals with OSA.

PAC-MI of Low-Frequency Theta Phase and High-Frequency Beta Amplitude During Wakefulness

Our study provides preliminary evidence for the increased theta-beta PAC-MI in the frontal and occipital regions during wakefulness. Beta oscillations are known to be closely associated with wakefulness,[39] and previous research has shown a correlation between beta activity and sleepiness levels,[49,50] suggesting that beta oscillations may serve as an indicator of sleep need.[51] Clinical studies on insomnia patients have reported increased decoupling of beta and gamma oscillation.[52] Additionally, research has found that patients with obesity-hypoventilation syndrome exhibit enhanced power in the slow-wave theta frequency range and high-frequency beta oscillations during wakefulness, which is associated with attention deficits, sleepiness, and nocturnal hypoxemia.[40,41] Intermittent hypoxia, characteristic of sleep apnea has complex, stage-specific effects on brain health. It disrupts hippocampal neurogenesis by reducing neural progenitors early and inhibiting neuron differentiation later, potentially through mechanisms involving the activation of HIF1a signaling, which subsequently enhances neuron generation following hypoxia.[53,54]

In this study, we found that moderate and severe OSA patients exhibited increased PAC of low-frequency theta and high-frequency beta during wakefulness compared to mild OSA patients, which was positively associated with hypoxemia-related measures. This suggests that PAC can serve as an electrophysiological marker reflecting the degree of hypoxemia in OSA patients. Further investigation into the synchronization of low-frequency and high-frequency brain activity in OSA patients during wakefulness, as well as its relationship with cognitive function, attention, and behavioral performance, will help us understand the physiological mechanisms underlying the perception of fatigue in OSA patients during wakefulness.

Limitations and Future Directions

There are several limitations and shortcomings in our study. Firstly, we did not include a healthy control group for comparison. Our findings reveal significant variability in certain data sets, potentially stemming from EEG interference and sensitivity limitations, coupled with an inadequate sample size. In future research, we plan to incorporate a larger sample size and include healthy individuals as controls to further validate and enhance our findings. Secondly, our

analysis of the brain's electrical signals only focused on certain areas since we only focused on PSG-related channels, which limited our examination to specific regions. Future studies should consider utilizing high-density resting-state and sleep EEG recordings to improve spatial resolution. Lastly, while our study focused on resting-state EEG data, event-related EEG signals during activities, such as the N-back task, may provide more detailed information on brain activity.

Conclusion

In this research, we analyzed the modulation index of various frequency combinations (1–45Hz) in the brain's electrical signals, as recorded by polysomnography (PSG) in patients with varying degrees of obstructive sleep apnea (OSA). Our study revealed a significant increase in phase-amplitude coupling (PAC) in the theta and beta frequency bands between the frontal and occipital cortices during N1 and wakefulness periods in OSA patients. The higher PAC-MI was positively correlated with indices of OSA severity and hypoxia indicators. Therefore, PAC may serve as a promising biomarker for OSA severity, and offer insights into the neurobiological mechanisms underlying cortical dysfunction in OSA patients. The present study provides new insights into the investigation of the associations between neural oscillations and respiratory hypoxia.

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Disclosure

The authors report no conflicts of interest for this work. The data on which this manuscript is based are open to researchers upon appropriate request.

References

1. Levy P, Kohler M, McNicholas WT, et al. Obstructive sleep apnoea syndrome. *Nat Rev Dis Primers*. 2015;1:15015. doi:10.1038/nrdp.2015.15
2. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. *Lancet*. 2014;383(9918):736–747. doi:10.1016/S0140-6736(13)60734-5
3. Wan XY, Zhao WR, Wu XR, Chen XY, Lei X. The brain imaging studies of obstructive sleep apnea: Evidence from resting-state EEG and fMRI. *Sheng Li Xue Bao*. 2019;71(5):760–768.
4. Puskas S, Kozak N, Sulina D, Csiba L, Magyar MT. Quantitative EEG in obstructive sleep apnea syndrome: A review of the literature. *Rev Neurosci*. 2017;28(3):265–270. doi:10.1515/revneuro-2016-0064
5. Zhang F, Wu X, Duan W, Wang F, Huang T, Xiang M. Influencing factors of daytime sleepiness in patients with obstructive sleep apnea hypopnea syndrome and its correlation with pulse oxygen decline rate. *Evid Based Complem Alter Med*. 2021;2021:6345734. doi:10.1155/2021/6345734
6. Yang Y, Wu W, Huang H, et al. Effect of CPAP on cognitive function in stroke patients with obstructive sleep apnoea: A meta-analysis of randomised controlled trials. *BMJ Open*. 2023;13(1):e060166. doi:10.1136/bmjopen-2021-060166
7. Blackwell T, Yaffe K, Laffan A, et al. Associations between sleep-disordered breathing, nocturnal hypoxemia, and subsequent cognitive decline in older community-dwelling men: The osteoporotic fractures in men sleep study. *J Am Geriatr Soc*. 2015;63(3):453–461. doi:10.1111/jgs.13321
8. Ercolano E, Bencivenga L, Palaia ME, et al. Intricate relationship between obstructive sleep apnea and dementia in older adults. *Gerosci*. 2024;46(1):99–111. doi:10.1007/s11357-023-00958-4
9. Behnoush AH, Khalaji A, Ghondaghsaz E, et al. Triglyceride-glucose index and obstructive sleep apnea: A systematic review and meta-analysis. *Lipids Health Dis*. 2024;23(1):4. doi:10.1186/s12944-024-02005-3
10. Zuzuarregui JRP, During EH. Sleep issues in Parkinson's disease and their management. *Neurotherap*. 2020;17(4):1480–1494. doi:10.1007/s13311-020-00938-y
11. Pontifex MB, Gwizdala KL, Parks AC, Billinger M, Brunner C. Variability of ICA decomposition may impact EEG signals when used to remove eyeblink artifacts. *Psychophysiol*. 2017;54(3):386–398. doi:10.1111/psyp.12804
12. Sutherland K, Sadr N, Bin YS, et al. Comparative associations of oximetry patterns in obstructive sleep apnea with incident cardiovascular disease. *Sleep*. 2022;45(12). doi:10.1093/sleep/zsac179.
13. Kovbasyuk Z, Ramos-Cejudo J, Parekh A, et al. Obstructive sleep apnea, platelet aggregation, and cardiovascular risk. *J Am Heart Assoc*. 2024;13(15):e034079. doi:10.1161/JAHA.123.034079
14. Zhang C, Wang YH, Li DX, et al. EEG power spectral density in NREM sleep is associated with the degree of hypoxia in patients with obstructive sleep apnea. *Nat Sci Sleep*. 2023;15:979–992. doi:10.2147/NSS.S433820
15. Fortin M, Lina JM, Desjardins ME, et al. Waking EEG functional connectivity in middle-aged and older adults with obstructive sleep apnea. *Sleep Med*. 2020;75:88–95. doi:10.1016/j.sleep.2020.06.008
16. D'Rozario AL, Cross NE, Vakulin A, et al. Quantitative electroencephalogram measures in adult obstructive sleep apnea - Potential biomarkers of neurobehavioural functioning. *Sleep Med Rev*. 2017;36:29–42. doi:10.1016/j.smrv.2016.10.003

17. Papaioannou O, Crespo LP, Clark K, et al. Is cortical theta-gamma phase-amplitude coupling memory-specific? *Brain Sci*. 2022;12(9). doi:10.3390/brainsci12091131.
18. Jensen O, Colgin LL. Cross-frequency coupling between neuronal oscillations. *Trends Cognit Sci*. 2007;11(7):267–269. doi:10.1016/j.tics.2007.05.003
19. Canolty RT, Knight RT. The functional role of cross-frequency coupling. *Trends Cognit Sci*. 2010;14(11):506–515. doi:10.1016/j.tics.2010.09.001
20. Fell J, Axmacher N. The role of phase synchronization in memory processes. *Nat Rev Neurosci*. 2011;12(2):105–118. doi:10.1038/nrn2979
21. Dimitriadis SI, Salis CI, Liparas D. An automatic sleep disorder detection based on EEG cross-frequency coupling and random forest model. *J Neural Eng*. 2021;18(4):046064. doi:10.1088/1741-2552/abf773
22. Hulsemann MJ, Naumann E, Rasch B. Quantification of phase-amplitude coupling in neuronal oscillations: Comparison of phase-locking value, mean vector length, modulation index, and generalized-linear-modeling-cross-frequency-coupling. *Front Neurosci*. 2019;13:573. doi:10.3389/fnins.2019.00573
23. Wang Y, Shi W, Yeh CH Sleep dynamic analysis technology based on cross-phase-amplitude transfer entropy in multiple brain regions. *Annu Int Conf IEEE Eng Med Biol Soc*. 2022; 2022:2953–2956.
24. Mikutta C, Feige B, Maier JG, et al. Phase-amplitude coupling of sleep slow oscillatory and spindle activity correlates with overnight memory consolidation. *J Sleep Res*. 2019;28(6):e12835. doi:10.1111/jsr.12835
25. Gouveris H, Koirala N, Anwar AR, et al. Reduced cross-frequency coupling and daytime sleepiness in obstructive sleep apnea patients. *Biol*. 2022;11(5). doi:10.3390/biology11050700.
26. Guo Y, Zhao X, Zhang X, et al. Effects on resting-state EEG phase-amplitude coupling in insomnia disorder patients following 1 Hz left dorsolateral prefrontal cortex rTMS. *Hum Brain Mapp*. 2023;44(8):3084–3093. doi:10.1002/hbm.26264
27. Gerstenslager B, Slowik JM. *Sleep Study*. StatPearls, Treasure Island. 2022.
28. Wang J, Xu J, Liu S, et al. Electroencephalographic activity and cognitive function in middle-aged patients with obstructive sleep apnea before and after continuous positive airway pressure treatment. *Nat Sci Sleep*. 2021;13:1495–1506. doi:10.2147/NSS.S322426
29. Berry RB, Budhiraja R, Gottlieb DJ, et al. American Academy of sleep M. rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. deliberations of the sleep apnea definitions task force of the American Academy of sleep medicine. *J Clin Sleep Med*. 2012;8(5):597–619. doi:10.5664/jcsm.2172
30. Pontifex MB, Miskovic V, Laszlo S. Evaluating the efficacy of fully automated approaches for the selection of eyeblink ICA components. *Psychophysiol*. 2017;54(5):780–791. doi:10.1111/psyp.12827
31. Yin Z, Zhu G, Liu Y, et al. Cortical phase-amplitude coupling is key to the occurrence and treatment of freezing of gait. *Brain*. 2022;145(7):2407–2421. doi:10.1093/brain/awac121
32. Caiola M, Devergnas A, Holmes MH, Wichmann T. Empirical analysis of phase-amplitude coupling approaches. *PLoS One*. 2019;14(7):e0219264. doi:10.1371/journal.pone.0219264
33. Wang X, Liu H, Kota S, et al. EEG phase-amplitude coupling to stratify encephalopathy severity in the developing brain. *Comput Meth Prog Biomed*. 2022;214:106593. doi:10.1016/j.cmpb.2021.106593
34. Hyafil A, Giraud AL, Fontolan L, Gutkin B. Neural cross-frequency coupling: connecting architectures, mechanisms, and functions. *Trends Neurosci*. 2015;38(11):725–740. doi:10.1016/j.tins.2015.09.001
35. Piantoni G, Astill RG, Raymann RJ, Vis JC, Coppens JE, Van Someren EJ. Modulation of gamma and spindle-range power by slow oscillations in scalp sleep EEG of children. *Int J Psychophysiol*. 2013;89(2):252–258. doi:10.1016/j.ijpsycho.2013.01.017
36. Sanchez E, El-Khatib H, Arbour C, et al. Brain white matter damage and its association with neuronal synchrony during sleep. *Brain*. 2019;142(3):674–687. doi:10.1093/brain/awy348
37. Rajeswari J, Jagannath M. Brain connectivity analysis based classification of obstructive sleep apnea using electroencephalogram signals. *Sci Rep*. 2024;14(1):5561. doi:10.1038/s41598-024-56384-9
38. Silverstein BH, Parkar A, Groenhout T, et al. Effect of prolonged sedation with dexmedetomidine, midazolam, propofol, and sevoflurane on sleep homeostasis in rats. *Br J Anaesth*. 2024;132(6):1248–1259. doi:10.1016/j.bja.2023.11.014
39. Gronli J, Rempe MJ, Clegern WC, Schmidt M, Wisor JP. Beta EEG reflects sensory processing in active wakefulness and homeostatic sleep drive in quiet wakefulness. *J Sleep Res*. 2016;25(3):257–268. doi:10.1111/jsr.12380
40. Greneche J, Krieger J, Erhardt C, et al. EEG spectral power and sleepiness during 24 h of sustained wakefulness in patients with obstructive sleep apnea syndrome. *Clin Neurophysiol*. 2008;119(2):418–428. doi:10.1016/j.clinph.2007.11.002
41. Sivam S, Poon J, Wong KKH, et al. Slow-frequency electroencephalography activity during wake and sleep in obesity hypoventilation syndrome. *Sleep*. 2020;43(2). doi:10.1093/sleep/zsz214.
42. Axmacher N, Henseler MM, Jensen O, Weinreich I, Elger CE, Fell J. Cross-frequency coupling supports multi-item working memory in the human hippocampus. *Proc Natl Acad Sci U S A*. 2010;107(7):3228–3233. doi:10.1073/pnas.0911531107
43. Nonoda Y, Miyakoshi M, Ojeda A, et al. Interictal high-frequency oscillations generated by seizure onset and eloquent areas may be differentially coupled with different slow waves. *Clin Neurophysiol*. 2016;127(6):2489–2499. doi:10.1016/j.clinph.2016.03.022
44. Lopez-Azcarate J, Tainta M, Rodriguez-Oroz MC, et al. Coupling between beta and high-frequency activity in the human subthalamic nucleus may be a pathophysiological mechanism in Parkinson's disease. *J Neurosci*. 2010;30(19):6667–6677. doi:10.1523/JNEUROSCI.5459-09.2010
45. Goutagny R, Gu N, Cavanagh C, et al. Alterations in hippocampal network oscillations and theta-gamma coupling arise before Abeta overproduction in a mouse model of Alzheimer's disease. *Eur J Neurosci*. 2013;37(12):1896–1902. doi:10.1111/ejn.12233
46. Netzer NCC, Ancoli-Israel SCC, Bliwise DL, et al. Principles of practice parameters for the treatment of sleep disordered breathing in the elderly and frail elderly: The consensus of the international geriatric sleep medicine task force. *Eur Respir J*. 2016;48(4):992–1018. doi:10.1183/13993003.01975-2015
47. Hutcheon EA, Vakorin VA, Nunes A, et al. Associations between spontaneous electroencephalogram oscillations and oxygen saturation across normobaric and hypobaric hypoxia. *Hum Brain Mapp*. 2023;44(6):2345–2364. doi:10.1002/hbm.26214
48. Hutcheon EA, Vakorin VA, Nunes AS, et A. Comparing neuronal oscillations during visual spatial attention orienting between normobaric and hypobaric hypoxia. *Sci Rep*. 2023;13(1):18021. doi:10.1038/s41598-023-45308-8
49. Stancin I, Frid N, Cifrek M, Jovic A. EEG signal multichannel frequency-domain ratio indices for drowsiness detection based on multicriteria optimization. *Sensors*. 2021;21:20. doi:10.3390/s21206932

50. Zhao W, Van Someren EJW, Li C, et al. EEG spectral analysis in insomnia disorder: A systematic review and meta-analysis. *Sleep Med Rev*. 2021;59:101457. doi:10.1016/j.smrv.2021.101457
51. Strijkstra AM, Beersma DG, Drayer B, Halbesma N, Daan S. Subjective sleepiness correlates negatively with global alpha (8-12 Hz) and positively with central frontal theta (4-8 Hz) frequencies in the human resting awake electroencephalogram. *Neurosci Lett*. 2003;340(1):17–20. doi:10.1016/S0304-3940(03)00033-8
52. Perlis ML, Smith MT, Andrews PJ, Orff H, Giles DE. Beta/Gamma EEG activity in patients with primary and secondary insomnia and good sleeper controls. *Sleep*. 2001;24(1):110–117. doi:10.1093/sleep/24.1.110
53. Khuu MA, Nallamothu T, Castro-Rivera CI, Arias-Cavieres A, Szujewski CC, Garcia Iii AJ. Stage-dependent effects of intermittent hypoxia influence the outcome of hippocampal adult neurogenesis. *Sci Rep*. 2021;11(1):6005. doi:10.1038/s41598-021-85357-5
54. Khuu MA, Pagan CM, Nallamothu T, et al. 3rd, Intermittent hypoxia disrupts adult neurogenesis and synaptic plasticity in the dentate gyrus. *J Neurosci*. 2019;39(7):1320–1331. doi:10.1523/JNEUROSCI.1359-18.2018