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ORIGINAL RESEARCH

Exploring the Arousal Intensity in Patients with Obstructive Sleep Apnea: Based on Odds Ratio Product

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Aim: Obstructive sleep apnea (OSA) is characterized by repetitive upper airway collapse during sleep, resulting in frequent cortical arousals. However, currently used frequency-based arousal metrics do not sufficiently capture the heterogeneity and clinical significance of arousal responses. The odds ratio product (ORP) is a novel electroencephalographic marker that provides a continuous assessment of sleep depth and has the potential to serve as an objective measure of arousal intensity.

Purpose: This study aimed to quantify the intensity of arousals in untreated OSA patients using the ORP, and to explore the relationships between arousal intensity, respiratory event features, and subjective sleepiness.

Patients and Methods: We retrospectively analysed data from 1057 adults with untreated OSA enrolled in the APPLES cohort. EEG spectral power was mapped to ORP values, and arousal intensity for each event was objectively calculated based on deviations in ORP from baseline. A total of 258,121 arousal events were included. Mixed-effects modelling was used to assess the impact of event type, duration, latency, sleep stage, position, and inter-individual variability on arousal intensity. Stepwise multiple regression explored associations between individual arousal intensity and subjective sleepiness.

Results: Arousal intensity increased significantly with the duration of preceding respiratory events, and was markedly higher than that of spontaneous arousals. The association between respiratory events and arousal intensity was stronger for apneas than for hypopneas, while deep sleep stage and lateral posture significantly reduced arousal response. Inter-individual variability was pronounced. Higher baseline arousal intensity was independently associated with increased subjective daytime sleepiness, after adjusting for known confounders.

Conclusion: ORP-derived arousal intensity provides a quantitative biomarker of cortical arousal. Arousal intensity is shaped by respiratory event characteristics, sleep architecture, and intrinsic individual traits. Although slight, arousal intensity is independently associated with subjective daytime sleepiness.

Keywords: obstructive sleep apnea, arousal intensity, odds ratio product, EEG, sleep fragmentation, sleepiness

Introduction

Arousal, in sleep medicine, describes the neurophysiological transition from sleep to a transient waking state. This process is primarily mediated by the brainstem reticular activating system (RAS) and is characterized by abrupt changes in electroencephalographic (EEG) activity.[1,2] In 1997, Davies et al first introduced the concept of "arousal intensity" in *Sleep Medicine Reviews*, postulating that impairment of cortical slow-wave sleep function may be the most significant factor contributing to recurrent pathological arousals and their daytime consequences.[3] Berry et al subsequently demonstrated, using pharyngeal pressure monitoring, a close association between the intensity of respiratory effort and the occurrence of cortical arousals.[4] However, due to the technical limitations in temporal and spatial resolution of neuroelectrophysiological tools and restricted diagnostic criteria at the time (eg, identification of arousals predominantly based on 3-second alpha rhythm in the EEG[3]), a consensus on quantifying arousal intensity remained elusive. Mainstream approaches continued to rely heavily on mechanical counting of EEG-based arousal events (such as hourly arousal

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index),[5] with limited capacity for precise quantification. This "frequency over quality" paradigm has resulted in arousal assessment systems lacking robust quantitative metrics, thus constraining the integration of multi-channel information and the application of individualized models such as endotype in OSA patients, where only categorical labelling is possible.[6]

With the advent of high frame-rate polysomnography (PSG) in the 21st century, analyses and definitions of arousal intensity are becoming increasingly diversified. Researchers such as Azarbarzin and Amatoury have subjectively annotated arousal intensity and established its strong association with respiratory stimuli.[7,8] Bahr et al adopted EEG amplitude-based methodologies, revealing a positive correlation between arousal intensity and the severity of OSA.[9] More recently, deep learning-based automated arousal detection algorithms have been introduced.[10,11] These advances highlight the fundamental limitations inherent in frequency-based arousal assessment, underscoring arousal intensity as a key quantitative variable for capturing arousal heterogeneity—a measurement domain whose developmental lag has become a critical bottleneck in sleep medicine precision.[12]

Obstructive sleep apnea (OSA) is typified by recurrent, complete or partial upper airway collapse during sleep, resulting in intermittent hypoxaemia, recurrent arousals and sleep fragmentation.[13] The estimated global prevalence of OSA is approximately 29%, affecting nearly one billion individuals.[14] In contrast to the infrequent spontaneous arousals observed in the healthy population, OSA patients experience regular, stimulus-driven arousals of quantifiable intensity, thereby providing a unique pathological model for exploring the relationship between arousal intensity and triggering events.[15]

The odds ratio product (ORP), developed by Younes et al, is a continuous metric to quantify sleep depth by analysing EEG signals. The ORP expresses sleep states on a continuum from 0 (deep sleep) to 2.5 (full wakefulness), enabling the characterisation of dynamic microstructural features of sleep on a sub-second scale.[16] ORP-based phenotyping and biomarker research have already demonstrated significant associations with cognition, excessive daytime sleepiness, and subjective sleep quality.[17–19]

In this study, we employ the internationally validated ORP as a quantitative index of arousal intensity, assessing its reliability under the natural pathological conditions of recurrent respiratory events in OSA patients. Specifically, we evaluate whether arousal intensity increases progressively with the escalation of respiratory stimuli, such as longer event duration or transitions from spontaneous arousal to hypopnea to apnea.

Through this systematic investigation, we aim to establish a robust definition and measurement framework for arousal intensity, laying a methodological foundation for the development of personalised therapeutic strategies in OSA. Clinically, this method can optimize the calculation of loop gain, thereby guiding pharmacological interventions for OSA—such as refining the selection of appropriate candidates for acetazolamide therapy.[20,21] Furthermore, this approach allows for the independent quantification of each patient's sleepiness burden specifically attributable to respiratory events, thus enabling a more precise evaluation of improvements in daytime sleepiness following OSA treatment.[19]

Materials and Methods

Data Sources and Sample Selection

This study utilized the APPLES (Adult Portable Sleep Study) dataset released by the National Sleep Research Resource (NSRR) platform.[22,23] The database originated from a multicenter randomized controlled trial aimed at evaluating the impact of continuous positive airway pressure (CPAP) therapy on neurocognitive function in patients with OSA. Data have been de-identified by removing all Protected Health Information (PHI) such as name, date of birth, and any other contact details. Each individual is identified only by a random apple-id variable. A total of 1057 adult participants (age ≥ 18 years) with untreated OSA were ultimately included in the study. All individuals completed baseline and follow-up polysomnography (PSG) using the Alice 4 system (Phillips Inc, America), subjective sleepiness scale assessments (Epworth Sleepiness Scale, ESS), and standardized questionnaire surveys. The overall analytical workflow is illustrated in Figure 1. Participants with missing PSG data or missing key questionnaire data were excluded from the analysis. The data used in this study were obtained from the NSRR under an approved Data Access and Use Agreement. All sleep scoring variables and instruments utilized are standard components of the NSRR datasets and are publicly available for

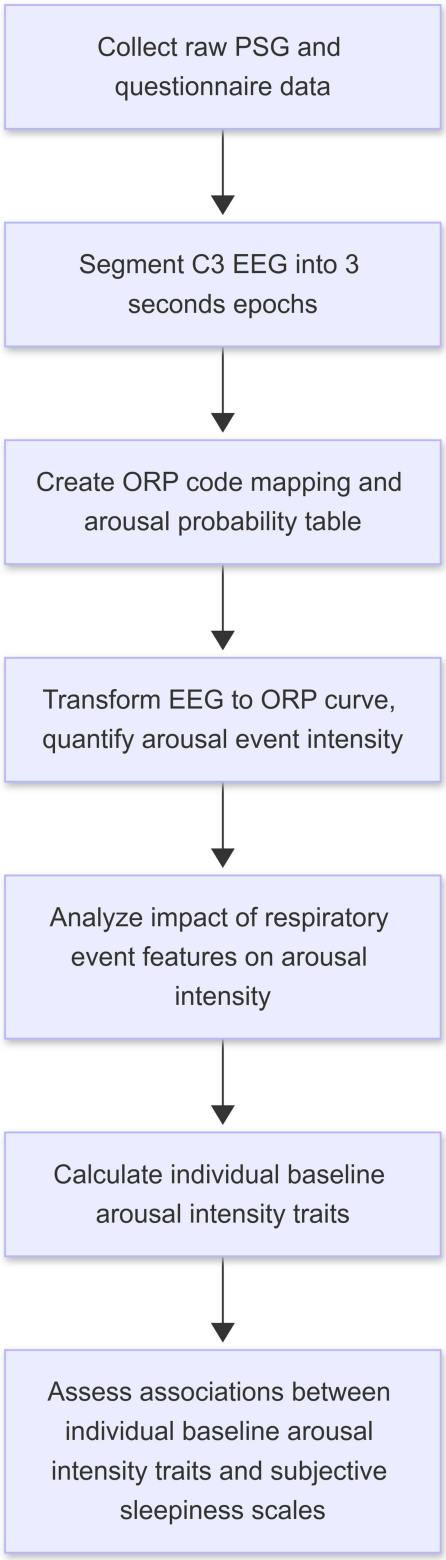

Figure 1 Overall Workflow of ORP-Based Arousal Intensity Analysis.

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research use; no additional licensing was required. Sleep and wakefulness were scored using Rechtschaffen and Kales criteria. Apnea and hypopnea were scored using AASM (1999) criteria. The method for sample size calculation is described in Supplementary Section 2. The analysis was approved by the Institutional Review Board of Beijing Tongren Hospital (TRECKY2024-135). Consent statement was waived by the ethics committee as this was a publicly available dataset.

ORP Probability Mapping and Validation

A sleep depth quantification model based on power spectral analysis and the ORP was constructed. Younes et al have described in detail the calculation steps of ORP.[16] The specific implementation steps are as follows: (1) Frequency band energy feature extraction: Each 3-second PSG segment was subjected to Fast Fourier Transform to extract the energy of four characteristic frequency bands—δ (0.3–2.3 Hz), θ (2.7–6.3 Hz), α-σ (7.3–14 Hz), and β (14.3–35 Hz).[16] (2) ORP reference table generation: The energy values of each frequency band were discretized into deciles (0–9), forming a four-digit feature code (C_i $(i = 1, \ldots, 10^4)$. For each code, the probability of arousal during PSG-annotated arousal events and wake periods was calculated as: $P_{arousal} = \frac{N_{arousal|C_i} + N_{wake|C_i}}{N_{total|C_i}}$. where $N_{arousal|C_i}$ and $N_{wake|C_i}$ represent the number of occurrences of the code during arousal events and wake epochs, respectively. The resultant ORP values are standardised by scaling the wake rate*2.5 to fall within the 0–2.5 continuum, where 0 corresponds to profound somnolence whilst 2.5 denotes full cognitive arousal.

Calculation of Arousal Intensity List

Based on the APPLES dataset overnight PSG recordings, an all-night ORP structural map was generated. Baseline arousal intensity was defined as the mean value during the 15-second period prior to each arousal event. The positive area of deviation (PAD) of the ORP curve from the baseline value during each arousal event was calculated and utilized as the index of arousal intensity. $Arousal_{intensity} = \int_{T_{onset}}^{T_{offset}} [ORP_{(t)} - ORP_{baseline}]\,dt$. The integration interval was defined from arousal onset (T_{onset}) to arousal offset (T_{offset}) (see Figure 2). Arousals occurring from 13 seconds before to 17 seconds after the end of a respiratory event were considered to be respiratory-related arousals.[24] Considering that prolonged

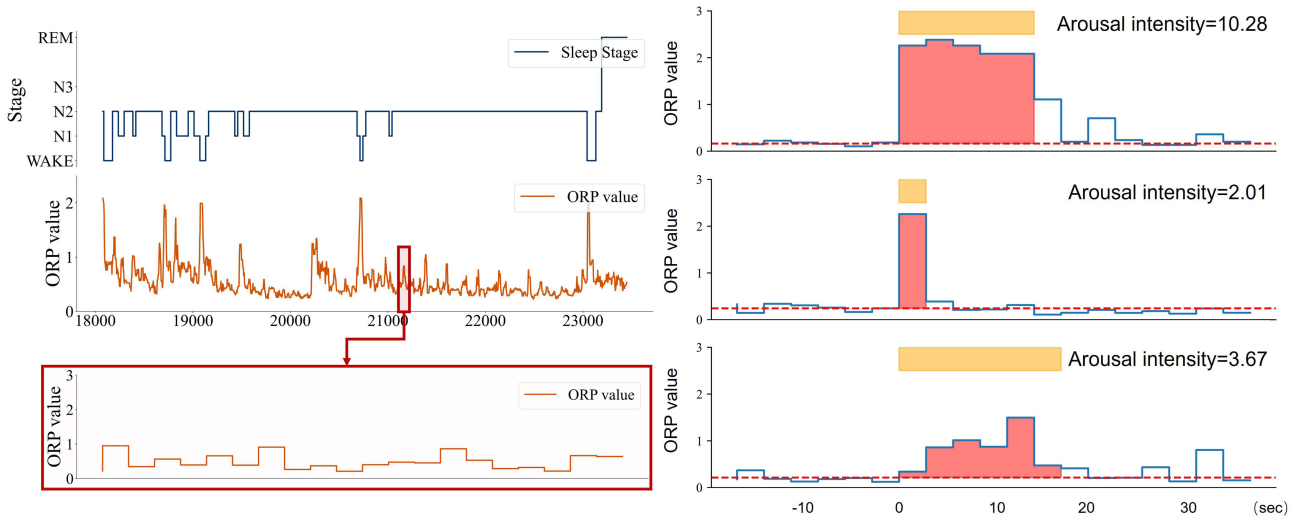

Figure 2 Schematic diagram of arousal intensity calculation. This diagram illustrates the process of ORP (Odds Ratio Product) calculation and arousal intensity assessment, as well as their significance. The upper left panel shows the temporal changes in sleep stages and corresponding ORP values. The analysis window highlighted by the red box is the same length as the standard window subsequently used for arousal event evaluation, but does not contain any arousal events. This window serves to demonstrate how the ORP time series displayed in the right panels is obtained and analysed. The three panels on the right depict ORP value changes during different arousal events; the yellow bars indicate manually scored arousal periods, and the red dashed lines represent the baseline arousal intensity. The red shaded areas indicate segments where ORP values sharply increase and exceed the threshold; by quantifying the magnitude and duration of these areas, arousal intensity can be measured. Higher values indicate stronger arousal.

arousals may be scored as wake periods, only arousals with a duration of 15 seconds or less were included in the final analysis.

Mixed-Effects Model for Validation of Arousal Intensity

The analysis included a subset of respiratory-arousal events with a respiratory event duration between 10 and 100 seconds and an absolute arousal latency within 15 seconds. A mixed-effects model was then constructed to predict arousal intensity. Subject ID was included as a random intercept to account for inter-individual variability, while fixed effects comprised respiratory event type, event duration, respiratory-arousal latency, sleep stage, position, desaturation duration, desaturation-arousal latency, and delta desaturation—all variables selected based on theoretical rationale and preliminary analyses.[25] The model was built following a stepwise optimization process: main effect variables were gradually introduced on the basis of the fixed random intercept, and variables without significant contributions to model fit or explanatory power were removed according to the Bayesian Information Criterion (BIC), in order to reduce redundancy and prevent overfitting. Subsequently, two-way interaction terms were introduced based on physiological plausibility and were also selected using BIC, ensuring that only those interactions that significantly improved model performance were retained.

Statistical Analysis

All statistical analyses were conducted using SPSS 26.0 and Python 3.9. Continuous variables are presented as mean ± SD or median [IQR], depending on normality assessed by the Shapiro–Wilk test. Categorical variables are summarized as counts and percentages. Group comparisons were performed using independent *t*-tests or Mann–Whitney *U*-tests for continuous data, and chi-square or Fisher's exact tests for categorical data, as appropriate. For analyses involving multiple groups, ANOVA or the Kruskal–Wallis test was used.

Mixed-effects models were built to assess the effects of respiratory event characteristics, sleep stage, and oxygen desaturation on arousal intensity, with subject ID as a random intercept. Model selection was based on stepwise optimization using the Bayesian Information Criterion (BIC), with physiologically plausible interactions included where relevant. Marginal R^2 values were reported.

To address multiple comparisons, correction methods such as Bonferroni or FDR were considered; where corrections were not applied, this was justified based on hypothesis-driven, limited contrasts. Multivariate stepwise regression was used to evaluate associations between baseline arousal intensity and subjective sleep outcomes, adjusting for potential confounders. All significance tests were two-sided with $\alpha = 0.05$.

Results

A total of 1057 subjects were enrolled, mainly patients with moderate to severe OSA. Detailed information is presented in Table 1.

Frequency Band Coding Characteristics of ORP

By examining the ORP values corresponding to the rank orders of different frequency bands (ie, frequency band coding, where higher values indicate closer proximity to wakefulness), we observed that the theta band rank was significantly negatively correlated with ORP ($R^2 = 0.28$, $P < 0.001$), while the beta band showed a significant positive correlation ($R^2 = 0.39$, $P < 0.001$) (see Figure 3).

Distribution of Arousal Intensity

A total of 258,121 arousal events were identified and their ORP arousal intensity calculated, with a mean intensity of 2.248 ± 3.283 (see Supplementary Figure 1). Analysis of variance revealed that inter-individual variability was greater than intra-individual variability (effect size (η^2): 0.257; Welch's F value: 18.89, $P < 0.001$), indicating significant differences in arousal characteristics between individuals. Among these, 171,346 arousals were associated with respiratory events. Restricted cubic splines were utilized to capture the associations between different types and durations of respiratory events and arousal intensity (see Supplementary Table 3). The results showed that: (1) Compared to

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Table 1 Baseline Characteristics of Participants in the APPLES Database

Characteristic	Value
Demographic Characteristics	
Gender (Male/Female)	698/359
Age (years)	52.00 [43.00, 61.00]
BMI (kg/m²)	30.74 [27.17, 36.19]
Years of Education (years)	16.00 [14.00–18.00]
Lifestyle Characteristics	
Moderate Caffeine User (Yes/No)	569/443
Moderate Alcohol User (Yes/No)	154/884
Current Smoker (Yes/No)	138/914
Illicit Drug User (Yes/No)	40/1004
Questionnaire	
Epworth Sleepiness Scale (ESS)	10.00 [7.00–13.00]
Morningness-Eveningess Questionnaire (MEQ)	56.00 [48.00–64.00]
Overnight Polysomnography Data	
Total Sleep Time (TST, min)	388.50 [345.00–422.00]
AHI (Apnea-Hypopnea Index, events/hour)	34.40 [20.20–54.30]
REM AHI (AHI during REM sleep, events/hour)	44.10 [25.10–63.00]
NREM AHI (AHI during NREM sleep, events/hour)	32.00 [16.80–55.00]
Arousal Index	24.87 [15.28–38.55]
Lowest Oxygen Saturation (Lowest SpO_2, %)	82.00 [77.00–87.00]
ODI (3% Oxygen Desaturation Index, events/hour)	19.60 [8.30–38.30]

Notes: Continuous variables are presented as median [interquartile range], and categorical variables as counts (Yes/No or Male/Female). "Moderate caffeine/alcohol user" is defined as >7 Servings/Week.
Abbreviation: BMI, body mass index.

spontaneous arousals, event-related arousals exhibited higher arousal intensity (2.24 ± 2.50 vs 1.91 ± 2.68, $P < 0.001$); (2) Arousal intensity exhibited a gradual increase with the prolongation of respiratory event duration; (3) Obstructive events had a relatively lower and more stable impact (for hypopnea, arousal ORP increased by 0.365 ± 0.024 as event duration extended from 14.5 to 25 seconds; for obstructive apnea, ORP increased by 0.840 ± 0.032 from 15 to 26 seconds), whereas mixed and central events exerted a larger and more variable influence (for mixed events, ORP increased by 0.778 ± 0.141 from 20.125 to 31 seconds; for central events, ORP increased by 0.702 ± 0.146 from 14.5 to 21 seconds; see Figure 4). (4) Arousal intensity in both the left and right lateral sleeping positions was significantly lower than in the supine position (Left: 1.987 ± 2.582; Right: 2.004 ± 2.550 vs Supine: 2.190 ± 2.560, both $p < 0.001$) (see Supplementary Figure 2).

Mixed Effects Model Analysis of Factors Influencing Arousal Intensity

After applying the selection criteria, a total of 142,154 event-arousal pairs (a subset of respiratory-arousal events) were included in the analysis. Respiratory event latency and desaturation event latency were excluded in the model; The findings were as follows: (1) The main effects of respiratory event types were statistically significant, with mixed apnea ($\beta = 0.436$, $P < 0.001$), central apnea ($\beta = 0.322$, $P < 0.001$), and obstructive apnea ($\beta = 0.249$, $P < 0.001$) showing higher values compared to hypopnoea; (2) As respiratory event duration increased, arousal intensity significantly increased across all event types ($\beta = 0.118$, $P < 0.001$). (3) Furthermore, compared to hypopnoea, the positive association between event duration and arousal intensity was more pronounced for mixed apnea ($\beta = 0.362$, $P < 0.001$), central apnea ($\beta = 0.500$, $P < 0.001$), and obstructive apnea ($\beta = 0.220$, $P < 0.001$); (4) Deeper sleep stages were associated with significantly reduced arousal intensity ($\beta = -0.597$, $P < 0.001$). In addition, the impact of oxygen desaturation on arousal intensity was significantly moderated by sleep stage (interaction: $\beta = 0.094$, $P < 0.001$). Specifically, greater oxygen desaturation was associated with higher arousal intensity, and this association was amplified in deeper sleep stages; (5) Both desaturation duration ($\beta = 0.061$, $P < 0.001$) and delta desaturation ($\beta = -1.182$, $P < 0.001$) were significant predictors of arousal intensity; (6) Significant inter-individual

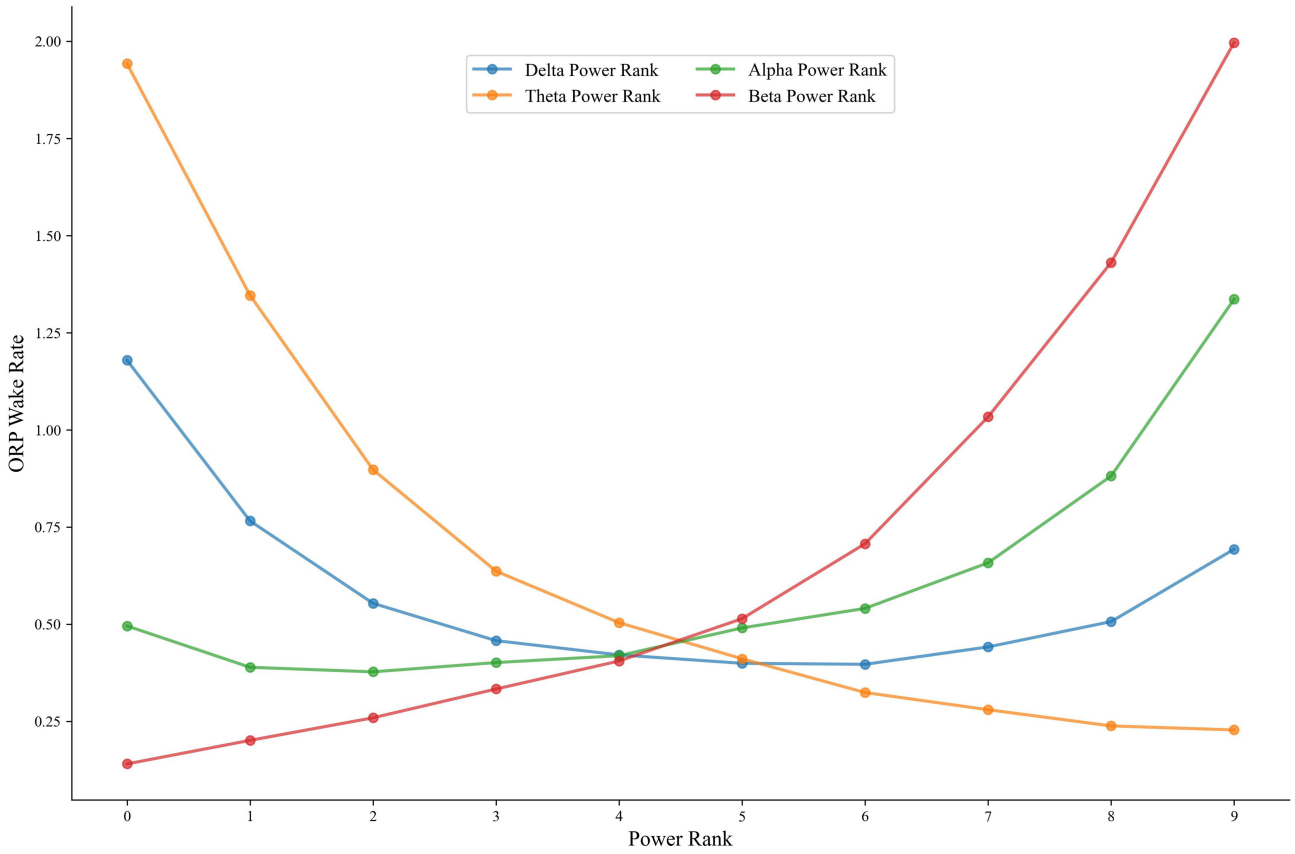

Figure 3 ORP values at different frequency band ranks. The x-axis shows the power rank of each EEG frequency band (0 = lowest, 9 = highest), and the y-axis shows the median ORP wake rate, an indicator of proximity to wakefulness. Higher theta power rank was significantly associated with lower ORP ($R^2 = 0.28$, $P < 0.001$), while higher beta power rank was significantly associated with higher ORP ($R^2 = 0.39$, $P < 0.001$).

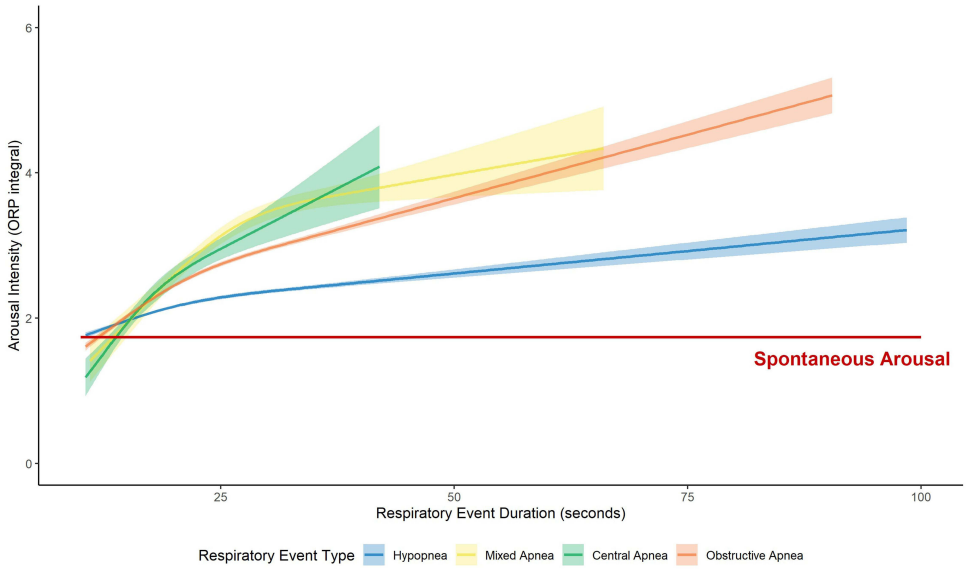

Figure 4 RCS Curves of Arousal Intensity by Respiratory Event Type. The x-axis represents the duration of respiratory events (seconds), and the y-axis shows arousal intensity. Curves are color-coded for hypopnea, mixed apnea, central apnea, and obstructive apnea. The red line indicates the arousal threshold for spontaneous arousal.

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Table 2 Multivariate Stepwise Regression Analysis of Sleepiness and Related Factors

Outcome Variable	Key Predictors in Final Model (in Entered Order)	Std. β	p value	Adjusted R^2
MEQ Total Score	Age, Gender, Nasal Congestion, Arousal Intensity, Cardiovascular, Anaemia, Cancer, Education	0.067	0.021	0.136
Unrested During Day	Age, Gender, COPD, Arousal Intensity, Nasal Congestion, Alcohol, Caffeine	0.082	0.006	0.115
Daytime Sleepiness	Age, Gender, Arousal Intensity, Allergy Rhinitis, Cancer, Arousal Index	0.104	0.001	0.070
ESS Total Score	BMI, Cardiovascular, Arousal Intensity, Alcohol, AHI, Arousal Index	0.066	0.035	0.037

Notes: "Std. β" refers to the standardized regression coefficient of the predictor "Arousal Intensity" in the final stepwise model. "p value" reflects the statistical significance for "Arousal Intensity". "Adjusted R^2" indicates the proportion of variance explained by the final model.
Abbreviations: MEQ, Morningness–Eveningness Questionnaire; ESS, Epworth Sleepiness Scale; BMI, body mass index; AHI, apnea–hypopnea index; COPD, chronic obstructive pulmonary disease.

variability in arousal intensity was present, as indicated by a random intercept variance of 0.679 (SD = 0.824). Overall, the model explained approximately 18.2% of the total variance in arousal intensity. Details of the model selection and final formula are provided in Supplementary Section 1 and Supplementary Tables 1 and 2.

Individual Arousal Intensity Characteristics and Subjective Sleepiness

Based on the above mixed-effects model, arousal intensity for each subject was calculated. Multivariate stepwise regression analysis was used to evaluate the effects of baseline arousal intensity and other clinical predictors on subjective and objective sleep outcomes in participants (Table 2). The list of predictors included in the stepwise regression is provided in Supplementary Table 4. Notably, arousal intensity showed a significant independent positive effect on both the ESS (β = 0.066, P = 0.035) and the MEQ (β = 0.067, P = 0.021). As an independent variable, arousal intensity was also significantly associated with most other sleepiness-related indicators, including subjective daytime sleepiness (β = 0.104, P = 0.001) and unrested during day (β = 0.082, P = 0.006). These associations remained robust after adjusting for traditional confounding factors such as age, gender, BMI, AHI, and medical history.

Discussion

This study is the first to utilize the clinically validated ORP as a continuous measure of sleep depth to objectively assess arousal responses to respiratory events in patients with OSA. The findings demonstrate that arousal intensity increases significantly with the prolongation of respiratory events, and that central and mixed events trigger stronger and more variable arousal responses. Furthermore, although the effect size was relatively small, individual arousal intensity characteristic is identified as independent risk factors for subjective sleepiness.

In contrast to traditional indices that only reflect event frequency, such as the microarousal index, ORP provides a more refined and continuous quantification of arousal intensity.[26] By calculating the positive area deviation (PAD) of the ORP curve during arousals, this method not only accurately captures changes in wakefulness status, but also, for the first time, offers a quantitative approach to the concept of "arousal intensity". Compared to the manually annotated method used by Azarbarzin's group[27] and the single EEG amplitude metric used by Bahr et al[9] the ORP-PAD approach presents three major advantages: (1) integration of multi-band EEG features; (2) second-level time-domain integration for quantifying arousal intensity; and (3) dynamic modelling of the stimulus–response intensity relationship. This framework provides an innovative biomarker-based method to support the "continuous sleep architecture" hypothesis proposed by Younes et al and enables a precise characterization of arousal responses to different types of respiratory events.[26]

Differences in Frequency Band Encoding Characteristics of ORP

By analysing power across multiple EEG frequency bands, ORP offers a refined and dynamic index of sleep depth in real-time.[28] Studies have shown that different frequency components within the ORP are associated with wake probability, but the direction of effect varies by band: decreases in theta power and increases in beta power are both typically linked to greater alertness, which is in line with interpretations of traditional indices like the bispectral index (BIS).[29]

However, delta and alpha band powers demonstrate a more complex, context-dependent influence—either increasing or decreasing these bands can elevate the likelihood of arousal, depending on the underlying EEG pattern. For instance, Younes et al observed that when the wake probability predicted by the other three bands is low, higher delta power actually further reduces wake probability, but conversely, if the initial probability is high, increasing delta further raises the risk of arousal.[16] The alpha band behaves similarly: across a variety of backgrounds and in interaction with other frequencies, both high and low alpha power can enhance the chance of arousal.[30,31] This helps to reconcile previous inconsistent findings, for example: in pre-sleep wakefulness when eyes may still be open, alpha power falls as alertness actually increases,[32] while during arousals triggered by external stimuli (such as respiratory events), alpha power can also drop rapidly.[33]

In summary, theta encodes the sleep process, beta reflects wakefulness, while both upward and downward shifts in delta and alpha may, in suitable contexts, heighten arousal risk.[27,34] By integrating these multidimensional dynamics, ORP surpasses BIS and other single-parameter indices in representing fluctuations in sleep depth.[16,29]

Variability and Distribution of Arousal Intensity

This study demonstrates that arousal intensity not only exhibits high intra-individual reproducibility (ie, stable distribution across nights within the same subject) but also shows significant inter-individual heterogeneity. The distribution of arousal intensity in most patients deviates markedly from a normal (Gaussian) distribution, instead exhibiting a pronounced rightward skew, as illustrated in Supplementary Figure 1. Younes et al revealed distinct ORP spectral patterns across subjects through multidimensional EEG biomarker analysis, with these characteristics demonstrating robust temporal stability during multi-night PSG.[26] Notably, the progressive deepening of sleep stages (W→REM→N1→N2→N3) exerts a regulatory effect on arousal response intensity: Bonnet et al quantitatively showed that identical stimuli elicited 40–60% weaker arousal responses during deep sleep (N3) compared to lighter stages (N1-N2) using a graded stimulation paradigm.[35,36] Our mixed effect model analysis confirms the neurodynamic basis of this phenomenon.

The Relationship Between Arousal Intensity and the Type and Duration of Respiratory Events

Arousal intensity is closely related to the type and duration of respiratory events. Specifically, the longer the duration of obstructive events, the higher the arousal intensity tends to be. Mechanistically, the type and duration of respiratory events are essentially measurable measures of stimulus strength—in general, more severe and prolonged events reflect a more adverse chemical internal environment, thereby eliciting stronger stimuli imposed on the body.[37] Compared to the approach of evaluating arousal intensity solely by EEG amplitude as in Bahr et al, our study not only confirmed the positive association between arousal intensity and the duration of respiratory events, but also further demonstrated that obstructive apneas, compared to hypopneas, elicit a much stronger arousal response.[9]

Central and mixed apnoeic events are often associated with more intense and variable arousal responses, the core pathophysiological mechanism of which lies in the cyclical instability of brainstem respiratory control. Such instability causes fluctuations in respiratory drive and may lower arterial carbon dioxide tension ($PaCO_2$) below the apnoeic threshold, thereby precipitating primary central sleep apnea. Following the onset of an apnoeic event, the consequent accumulation of carbon dioxide increases chemoreceptor input to the brainstem, which in turn activates cortical arousal and respiratory motor neurons to restore ventilation.[37] Notably, due to the absence of mechanical stimuli such as negative intrathoracic pressure, central and mixed events are more frequently associated with pronounced hypoxaemia and hypercapnia, manifesting as marked increases in ventilation and intense autonomic activation.[4,38] Nevertheless, inter-individual differences in arousal threshold and physiological expression are substantial, resulting in high variability of arousal intensity.[4,5] Experimental data demonstrate that the activity level of noradrenergic neurons in the locus coeruleus (LC) directly influences the arousal threshold; higher LC activity confers heightened sensitivity to chemical stimuli, which may underlie the considerable variability in arousal intensity observed in central events.[39]

Mixed events typically reflect coexisting central dysregulation and obstructive burden; this dual mechanism reduces upper airway muscle coordination. Upon arousal, the imperative to re-open the airway intensifies, and relevant muscle groups (such as tonic and phasic dilator muscles) may exhibit asynchronous activation patterns, resulting in more intense and heterogeneous arousal responses across individuals.[2,38,40]

Posture, Desaturation and Arousal Latency in Relation to Arousal Intensity

Our study reveal that lateral posture was consistently associated with significantly lower arousal intensity compared to the supine posture. This finding is physiologically plausible, as the supine position is well known to predispose individuals to more severe upper airway collapse due to gravitational effects on pharyngeal tissues, increased tongue base displacement, and reduced upper airway calibre.[25,41,42]

Similar to the duration of respiratory events, desaturation duration also showed a positive association with arousal intensity, which is consistent with the conclusions of previous studies.[9] Interestingly, contrary to our intuition, although delta desaturation exhibited a weak positive correlation with arousal intensity, it emerged as a protective factor for arousal intensity in the mixed-effects model. This phenomenon may be explained by the strong physiological correlations among delta desaturation, respiratory events, and desaturation duration in the mixed-effects model. When these covariates are controlled for (ie, at the same event duration), the regression coefficient of delta desaturation on arousal intensity becomes negative, suggesting an apparent "protective" effect.

In 2014, Eckert and Younes proposed that airway reopening and cortical arousal represent two distinct physiological pathways. They suggested that the stimulus for airway reopening may serve as a trigger for arousal, and that the temporal proximity of these two events may be merely coincidental.[43] Our findings also support this perspective, showing that the latency of arousal relative to respiratory and desaturation events is not significantly associated with arousal intensity. Our previous research has demonstrated that cortical arousals are associated with a more negative esophageal pressure compared to respiratory events that terminate without arousal.[44] However, due to the absence of esophageal pressure monitoring and diaphragmatic electromyography in the present study, we lacked direct physiological calibration of respiratory event intensity. As a result, we were unable to establish the precise dose–response relationship between the stimulus at the arousal threshold and the corresponding arousal intensity—that is, whether a greater arousal intensity requires a larger negative esophageal pressure to be triggered.

Mechanism of Individual Arousal Intensity and Subjective Sleepiness

Individual arousal intensity not only constitutes an objective physiological phenotype, but is also closely linked to daytime sleepiness, and subjective sleep quality.[45–47] Our study demonstrates that an elevated arousal intensity often reflects reduced deep sleep, leading to impaired restorative sleep, which in turn manifests as excessive daytime sleepiness. Notably, these associations remain robust even after adjusting for confounders such as age, gender and BMI. Younes et al categorised overnight ORP curves into nine distinct types and demonstrated that ORP reliably characterises nocturnal sleep structure and strongly correlates with subjective assessments of sleep quality and daytime sleepiness.[48,49] Mechanistically, frequent or intense arousals fragment the normal sleep architecture, resulting in the cortex remaining at a heightened wakefulness status.[45,50,51] This state disrupts physiological sleep composition by increasing the proportion of light sleep and wakefulness and reducing deep sleep, thereby significantly compromising the feeling of refreshment and overall perceived sleep quality.[11,12,52] These findings further corroborate the clinical value of ORP as a biomarker of arousal intensity, and provide mechanistic insight into the relationship between sleep fragmentation, subjective sleep experience, and daytime dysfunction.[19,53,54] Although arousal intensity is an independent predictor of daytime sleepiness, its limited explanatory power suggests that relying solely on ORP-derived arousal intensity may not be sufficient to accurately predict improvements in sleepiness after OSA treatment.

Arousal intensity plays an indirect role in the individualized treatment of OSA. Current pharmacological therapies for OSA rely on the PALM system to select suitable candidates, such as using acetazolamide to lower loop gain or zolpidem to raise the arousal threshold.[55–57] However, the PALM system defines arousal in a binary "all-or-none" manner, disregarding differences in arousal intensity.[6,58] The calculation of ORP-derived arousal intensity is straightforward and can directly replace the original $V_{arousal}$ parameter, thereby improving the accuracy of model fitting.

Limitation

This study has several limitations. First, without simultaneous esophageal pressure monitoring or diaphragmatic EMG, we could not directly calibrate the physiological intensity of respiratory events. As a result, we were unable to determine whether greater arousal intensity is triggered by larger negative esophageal pressure or by other stimuli, such as chemical factors; Second, our reliance on single-night PSG data limits the assessment of the long-term stability and generalizability of the measurement, as individual traits may fluctuate across different nights.[59] Furthermore, it makes it difficult to compare differences between nights, such as evaluating the influence of factors like the first-night effect;[60] Third, our mixed-effects model explained only a small fraction of the variance in arousal intensity, suggesting that additional unmeasured factors may influence individual arousal responses. Future studies should employ more comprehensive approaches, particularly label-free feature processing methods, to address these limitations and further elucidate the mechanisms underlying arousals and respiratory event in OSA. Finally, as the APPLES cohort excluded patients with mild OSA (AHI < 10) and predominant CSA, the generalizability of our findings may be limited.

Conclusion

This study is the first to utilize ORP as a continuous measure of sleep depth to objectively quantify the arousal intensity during respiratory events in patients with OSA. Our results show that arousal intensity increases with the duration and severity of respiratory events, and is especially elevated in central and mixed apnea. In contrast, lower arousal intensity is observed during deeper sleep stages. Additionally, individuals with higher arousal intensity tended to report greater subjective daytime sleepiness, but this association was modest and influenced by multiple factors.

Abbreviations

OSA, obstructive sleep apnea; ORP, odds ratio product; EEG, electroencephalogram; PSG, polysomnography; PAD, positive area deviation; CPAP, continuous positive airway pressure; NSRR, National Sleep Research Resource; APPLES, Apnea Positive Pressure Long-term Efficacy Study; AHI, apnea-hypopnea index; REM, rapid eye movement; NREM, non-rapid eye movement; TST, total sleep time; SpO_2, pulse oximetric oxygen saturation; ODI, 3% oxygen desaturation index; ESS, Epworth Sleepiness Scale; MEQ, Morningness-Eveningness Questionnaire; RCS, restricted cubic spline; AIC, Akaike information criterion; BIC, Bayesian information criterion; RAS, reticular activating system; LC, locus coeruleus; BIS, bispectral index.

Data Sharing Statement

The APPLES dataset is all publicly available on reasonable request in National Sleep Research Resource (https://sleepdata.org).

Ethical Statement

The data used in this study were obtained from the NSRR under an approved Data Access and Use Agreement. The dataset mentioned above was all publicly available, and the analysis was approved by the Institutional Review Board of Beijing Tongren Hospital (TRECKY2024-135). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Author Contributions

Y.S.: Conceptualization, Investigation, Study design, Data curation, Software, Formal analysis, Writing – original draft, Visualization. J.L.: Validation, Software, Visualization, Writing – review & editing. X.G.: Data curation, Methodology,

Writing – review & editing. Y.L.: Methodology, Writing – review & editing, Supervision, Funding acquisition. D.H.: Writing – review & editing, Resources, Study design, Project administration. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors report no conflicts of interest in this work.

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