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Mechanism of neural oscillations and their relationship with multiple cognitive functions and mental disorders

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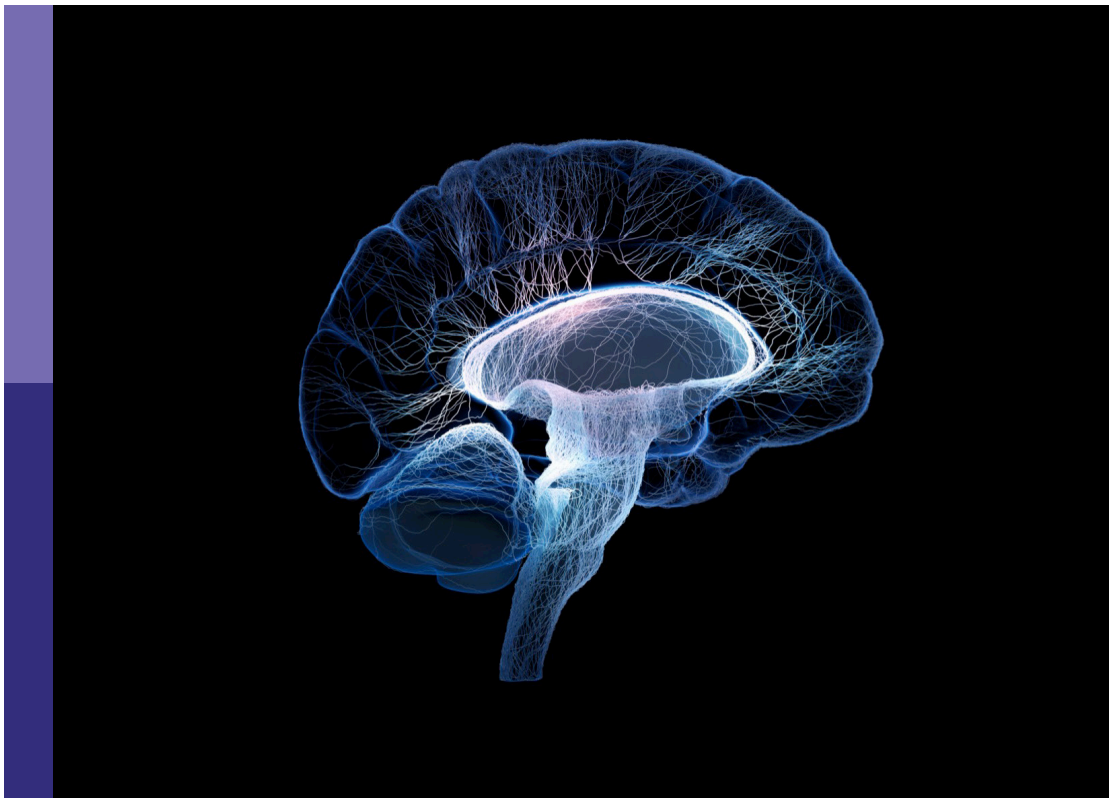

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Mechanism of neural oscillations and their relationship with multiple cognitive functions and mental disorders

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Editorial: Mechanism of neural oscillations and their relationship with multiple cognitive functions and mental disorders

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KEYWORDS

neural oscillation, cognitive function, mental disorder, neuroelectrophysiology, power spectrum

Editorial on the Research Topic
Mechanism of neural oscillations and their relationship with multiple cognitive functions and mental disorders

Neural oscillations serve as a crucial biological bridge between the micro and macro levels of brain activity (Han et al., 2021a; Buzsáki and Vöröslakos, 2023). These oscillations play key roles in various functions (Han et al., 2021c; Lin et al., 2024). Moreover, abnormal neural oscillations are recognized as potentially influential factors in the development of a wide range of mental disorders (Han et al., 2022a; Wang et al., 2024; Zikereya et al., 2024). However, our understanding of the mechanisms underlying neural oscillations and their functional roles in different cognitive functions and mental disorders remains limited. Through this Research Topic, 10 related papers in the field are published, including research and review papers in different aspects. Although we have not yet been able to fully answer the question of neural oscillation mechanisms, these studies have nonetheless made significant progress, advancing step by step toward this goal.

Mood disorders are increasingly receiving attention from researchers [major depression diorder (MDD) or bipolar disorder (BD)]. In this Research Topic, there are seven papers involving mood disorders, which provide deeper insights into our understanding of their oscillatory mechanisms. Liu et al. analyzed EEG signals to enhance the diagnosis of MDD. By examining resting-state EEG under both eyes-closed and eyes-open conditions, asymmetries in band power between hemispheres were key predictors of MDD. This multi-region, multi-condition approach improves diagnostic accuracy for MDD, suggesting EEG could be a valuable tool for objective MDD diagnosis and treatment planning. Zhang et al. explores how alpha oscillations in the medial occipital cortex (MOC) mediate the relationship between depression severity and suicide risk in MDD. It found that higher depression severity increases suicide risk, while greater MOC alpha power serves as a protective factor. Specifically, MOC alpha power partially mediates the effect of depression severity on suicide risk, with a decrease in alpha power linked to higher suicide risk. Wang et al. investigates the alterations in EEG functional connectivity (FC) in individuals with MDD compared to healthy controls (HCs). Using resting-state EEG and phase locking value (PLV) analysis across five frequency bands (theta, alpha, and beta), the study found lower FC in MDD patients in certain brain regions, notably in the right temporal-left occipital cortex. No significant correlation was found between FC differences and depression severity. The study suggests EEG-based FC could be a promising tool for objective MDD diagnosis. Su et al. reviews the latest resting-state EEG (rsEEG) findings in BD, highlighting abnormal oscillations across multiple frequency bands (delta, theta, beta, and gamma), often

marked by increased power. These abnormalities suggest widespread neural dysfunction. However, alpha oscillations showed more variability, potentially influenced by disease severity and sample diversity. The review stresses the importance of standardized experimental designs, considering factors like gender, age, medication, and methodology. These insights could help improve BD diagnosis and treatment.

Moreover, animal experiments with gamma-band activities also contribute a lot in this field (Han et al., 2021b, 2022b), Bergosh et al. explores the use of ketamine (KET) and medial prefrontal cortex deep brain stimulation (mPFC DBS) as treatments for depression in a rodent model. It examines how electrophysiological biomarkers, such as spectral parameters and sample entropy in local field potentials (LFP), correlate with antidepressant-like behaviors. Results suggest that changes in theta and gamma activity, along with sample entropy, may serve as biomarkers for depression severity and treatment efficacy, supporting both KET and mPFC DBS as potential therapeutic strategies. Neuhäusel and Gerevich investigates the sex-specific effects of the NMDA receptor antagonist MK-801 on hippocampal gamma oscillations in rats. It finds that female rats are more sensitive to MK-801, showing increased gamma oscillation power, impaired recognition memory, and increased stereotypic behaviors. In contrast, male rats did not exhibit these changes, highlighting sex differences in the pharmacological effects of NMDA antagonists, which could inform future research into treatments for neuropsychiatric disorders like schizophrenia and depression.

In recent years, physical activity has also attracted increasing attention from researchers (Wang et al., 2022). However, it is still not fully understood how neural oscillations are influenced by different types of exercise. In our Research Topic, there are two relevant review papers that deserve our attention. Li et al. explores how physical exercise (PE), including both aerobic and resistance training, promotes brain plasticity through neural oscillations. PE enhances cognitive function by modulating brain activity, especially in frequency bands like delta, theta, alpha, beta, and gamma. Exercise increases neurotrophic factors like BDNF and IGF-1, which support brain structures like the hippocampus and prefrontal cortex. The review emphasizes how different types of exercise, such as mind-body practices, affect neural activity, offering therapeutic potential for age-related cognitive decline and neurodegenerative diseases. Peng et al. explores Beta-band corticomuscular coherence (Beta-CMC), which refers to the synchronization of brain and muscle activity during movement. Beta oscillations (12–30 Hz) are crucial for motor control, influencing movement planning and execution. The review discusses Beta-CMC's role in various conditions such as motor disorders, rehabilitation, and athletic performance. It highlights the mechanisms of Beta oscillations in the sensorimotor system and their clinical applications, particularly for neurofeedback and personalized neuromodulation, aiming to improve therapeutic and athletic outcomes.

In sum, this Research Topic provides valuable new insights into the complex mechanisms of neural oscillations in the context of mood disorders, animal models, and physical exercise. Although much remains to be understood, these studies contribute significantly to advancing our knowledge and offer promising therapeutic directions.

Author contributions

CH: Writing – original draft, Writing – review & editing.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EEG-based major depressive disorder recognition by neural oscillation and asymmetry

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Background: Major Depressive Disorder (MDD) is a pervasive mental health issue with significant diagnostic challenges. Electroencephalography (EEG) offers a non-invasive window into the neural dynamics associated with MDD, yet the diagnostic efficacy is contingent upon the appropriate selection of EEG features and brain regions.

Methods: In this study, resting-state EEG signals from both eyes-closed and eyes-open conditions were analyzed. We examined band power across various brain regions, assessed the asymmetry of band power between the hemispheres, and integrated these features with clinical characteristics of MDD into a diagnostic regression model.

Results: Regression analysis found significant predictors of MDD to be beta2 (16–24 Hz) power in the Prefrontal Cortex (PFC) with eyes open ($B = 20.092$, $p = 0.011$), beta3 (24–40 Hz) power in the Medial Occipital Cortex (MOC) ($B = -12.050$, $p < 0.001$), and beta2 power in the Right Medial Frontal Cortex (RMFC) with eyes closed ($B = 24.227$, $p < 0.001$). Asymmetries in beta1 (12–16 Hz) power with eyes open ($B = 28.047$, $p = 0.018$), and in alpha (8–12 Hz, $B = 9.004$, $p = 0.013$) and theta (4–8 Hz, $B = -13.582$, $p = 0.008$) with eyes closed were also significant predictors.

Conclusion: The study confirms the potential of multi-region EEG analysis in improving the diagnostic precision for MDD. By including both neurophysiological and clinical data, we present a more robust approach to understanding and identifying this complex disorder.

Limitations: The research is limited by the sample size and the inherent variability in EEG signal interpretation. Future studies with larger cohorts and advanced analytical techniques are warranted to validate and refine these findings.

KEYWORDS

major depressive disorder, electroencephalography, neural oscillation, asymmetry, diagnostic regression model

1 Introduction

Major Depressive Disorder (MDD) has become one of the three leading causes for years lived with disability with more than 264 million people affected worldwide (James et al., 2018). For those affected, MDD means personal suffering, reduced functioning and quality of life, social withdrawal, risk for co-morbid medical condition and increased mortality risk (Kessler and Bromet, 2013). Traditional diagnostic practices for MDD, while valuable, rely on subjective assessments that may not adequately reflect the biological foundations of the disorder (Dean and Keshavan, 2017). This highlights the pressing need for objective biomarkers that can enhance diagnostic precision and inform personalized treatment strategies (Ivanets et al., 2021; Carrle et al., 2023).

Neurophysiological methods such as electroencephalography (EEG) have gained traction as potential tools for elucidating the neural correlates of MDD (Lei et al., 2022). EEG's high temporal resolution enables the detection of subtle changes in brain oscillations that are often associated with MDD, offering a window into the underlying neurophysiology of the disorder. The relevance of EEG in MDD diagnosis is further underscored by its potential to reveal altered spectral power within specific frequency bands linked to the disorder's emotional dysfunctions (Cao et al., 2022; Han et al., 2022; Teng et al., 2022; Huang et al., 2023; Kavanaugh et al., 2023; Han et al., 2023a). Despite these advances, challenges persist in translating these findings into clinical practice, with issues such as inter-individual variability and the influence of medication status affecting the utility of EEG as a standalone diagnostic tool (Watts et al., 2022). To accurately identify patients with MDD, researchers have explored various analysis methods for EEG signals. Hasanzadeh et al. (2019) integrated multiple nonlinear features to achieve a classification accuracy of up to 91.3%. Bai et al. (2021) employed the k-Nearest Neighbors (KNN) model to analyze the complexity features of the gamma band, reaching an accuracy of 79.63%, while a random forest classifier achieved an accuracy of 65.94% for the fractal dimension of the beta band.

EEG data, which quantifies cortical activity through time series analysis methods like fast Fourier transformation, is invaluable in studying MDD. Recent research has confirmed the significance of EEG frequency band power (Wang et al., 2023; Han et al., 2023b), particularly noting increased alpha and theta power in patients in the early stages of depression (Grin-Yatsenko et al., 2010). This supports the notion that specific EEG patterns, such as alpha activity, play a functional role in MDD and its treatment response. Moreover, the BDNF Val66Met polymorphism has been linked to EEG alpha power, with the MetMet variant associated with low-voltage alpha EEG in MDD patients, suggesting a genetic influence on EEG characteristics (Zoon et al., 2013). Research by Yang et al. (2023) supports the effectiveness of using power spectral density (PSD) features for examining EEG signals across frontal, temporal, and central regions. Their findings suggest that these combined regions yield the highest accuracy in detecting MDD.

Further studies indicate that depression affects the brain's hemispheres asymmetrically, leading to distinct patterns across various regions (Jiang et al., 2021). This asymmetry in brain activity is a critical aspect of how depression manifests and is detectable through EEG. Chang et al. (2011) reported the expected pattern of decreased alpha power at right frontal sites relative to the left, suggesting a hyperactive right and hypoactive left prefrontal cortex in depression. The assessment of resting-state EEG signals from different brain areas and frequency bands has been consistently highlighted as important, offering insights into the neural mechanisms behind emotional processes. Particularly significant is the practice of combining EEG data from both eyes-open and eyes-closed conditions into a single analytical model (Han et al., 2023b). This integrated approach provides a comprehensive understanding of brain activity, including its asymmetries, which is crucial for developing robust biomarkers for conditions like MDD (Ladeira et al., 2020). Despite its potential, the application of this integrative method in MDD research is still rare, emphasizing the need for further exploration in this area to enhance the diagnosis and understanding of depression.

In this study, we analyzed the resting-state EEG characteristics of individuals with MDD and healthy controls under both eyes-closed (EC) and eyes-open (EO) conditions. We focused on the neural oscillation of different brain regions and the asymmetry of band power between hemispheres. These features, along with clinical characteristics of the disease, were incorporated into a diagnostic regression model for MDD. In contrast to traditional EEG-based methods for MDD classification, which often focus on singular frequency band analysis or simple lateralization indexes, our approach represents a significant advancement. We integrate multi-regional band power assessments with hemispheric asymmetry analysis in both eyes-closed and eyes-open conditions, providing a more detailed picture of the brain's electrical activity. This method acknowledges the dynamic nature of EEG signals and their variability with different states of arousal, which has been overlooked in previous studies. By doing so, we aim to capture the intricate neural oscillation patterns that are more indicative of MDD, potentially leading to improved diagnostic accuracy.

2 Method

2.1 Participants

The study was conducted at Beijing Anding Hospital from July 2022 to May 2023. All patients receiving psychiatric services at the hospital during this period were consecutively invited to participate in the survey. The inclusion criteria consisted of age between 18 and 65 years, a diagnosis of MDD according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) and a total score of ≥17 on the 17-item Hamilton Depression Rating Scale (HDRS-17). Exclusion criteria included the presence of a severe and unstable medical or surgical condition, a history of alcohol or substance abuse/dependence, and a diagnosis of dementia or other evident cognitive impairments. Healthy controls (HCs) were recruited from the community through advertisements. The study protocol received approval from the Ethics Committee of Beijing Anding Hospital (Registration Number: 2020-106), and all participants provided written informed consent following a thorough explanation of the study details. This study has completed clinical registration on https://www.chictr.org.cn/ (Clinical Trial Registration Number: ChiCTR2200059053).

2.2 Data collection and measurements

The primary socio-demographic and clinical data were collected using a form designed for this study. We collected the basic demographic information of participants, including age and gender. The severity of the depressive and anxious symptoms was measured using the HDRS-17 and the Hamilton Anxiety Scale-14 (HAMA-14).

2.3 EEG signal acquisition and data processing

EEG signal acquisition was meticulously performed, capturing resting-state EEG data from participants through a structured protocol. Each participant underwent a sequence of resting-state recordings starting with a 10-min eyes-closed session, followed by a 30-s rest period, and concluding with a 10-min eyes-open session. The eyes-open recording was conducted with the participant seated comfortably in a chair, facing a monitor placed 100 cm away with a black background and a white fixation cross located the central line of sight. Participants were instructed to remain calm and relaxed, minimize head and limb movements, and consistently gaze at the fixation cross to reduce the impact of blinking and eye movements on the EEG signal.

Similarly, during the 10-min eyes-closed session, participants were asked to maintain a quiet, alert state. If a participant began to doze off, an auditory warning from the experimenter was issued. Any instances of warnings, opening eyes, or other non-resting states were marked and noted. Upon completion of the experiment, participants were assisted in washing off the conductive EEG paste from their scalp.

Data were obtained from 19 Ag/AgCl electrode channels using the advanced Neuracle system, which operates at a sampling rate of 1,000 Hz. While referencing the Cz electrode, we ensured that impedance was maintained below 50 kΩ, a level that our system's high-resolution amplifiers can accommodate without compromising data integrity. To control for potential distortion and fluctuations in both noise and signal, we implemented several measures: The EEG recording environment was carefully controlled for electrical and ambient noise. Participants were prepared adequately to minimize impedance, including skin preparation to reduce resistance. The Neuracle system was calibrated before each recording session to ensure optimal signal acquisition. Continuous monitoring of impedance levels was performed throughout the recording to detect and rectify any deviations promptly. Signal quality was assessed in real-time, with any segments affected by artifacts being marked for exclusion from subsequent analyses.

2.3.1 EEG preprocessing

EEG data preprocessing utilized the EEGLAB toolbox within MATLAB R2013a for bandpass filtering (1–40 Hz) and notch filtering (49–51 Hz), followed by downsampling to 500 Hz. Two-second epochs were employed for artifact rejection and further analysis. Eye movement artifacts were removed by independent component analysis.

Epochs with voltage excursions beyond ±150 μV were excluded. Subsequently, data were re-referenced to the average reference, and spectral power and asymmetry were computed for the 2-s epochs.

2.3.2 Power spectrum

Power spectrum analysis was conducted using a Fast Fourier Transform (FFT) algorithm to quantify brain activity in the frequency domain (Han et al., 2021a,b), with power represented by the average instantaneous power of the analytic signal. Relative power for each frequency band was determined by normalizing the absolute power to the total broadband power, encompassing delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta1 (12–16 Hz), beta2 (16–24 Hz), and beta3 (24–40 Hz). Electrodes were categorized into ten regions of interest (ROIs) for focused analysis: Prefrontal Cortex (PFC, including FP1, FP2, and Fz), Right Medial Frontal Cortex (RMFC, including Fz, F4, and F8), Left Medial Frontal Cortex (LMFC, including Fz, F3, and F7), Central Cortex (CC, including C3, C4, and Cz), Parietal Cortex (PP, including P3, P4, and Pz), Left Temporal Cortex (LT, including F7, T3, and T5), Right Temporal Cortex (RT, including F8, T4, and T6), Medial Occipital Cortex (MOC, including O1, Pz, and O2), Right Medial Occipital Cortex (RMOC, including P4, O2, and Pz), and Left Medial Occipital Cortex (LMOC, including P3, O1, and Pz).

2.4 Statistical analysis

Statistical analyses were performed with R version 4.0.3 and MATLAB 2013b. Group comparisons for demographic and clinical variables were conducted using chi-square tests and t-tests, with a significance level set at $p < 0.05$ (two-tailed). Binary logistic regression analyzed potential predictors of MDD, and the model's performance was validated using 10-fold cross-validation to ensure robustness. The receiver operating characteristic (ROC) curve analysis determined the optimal cut-off points for neural oscillation power values between MDD patients and healthy controls, calculating the area under the curve, sensitivity, and specificity. Pearson correlation was employed to examine the relationship between neural oscillation characteristics and symptom severity.

3 Results

3.1 Demographic and clinical characteristics of MDD and HC

We collected and analyzed data for 86 MDD patients and 83 healthy controls. The male-to-female ratios and age distributions did not differ significantly between the groups ($\chi^2 = 1.279$, $p = 0.258$ for gender; $t = -0.218$, $p = 0.827$ for age). There was no significant difference in education level between the two groups ($t = 0.44$, $p = 0.66$). The distribution of married and unmarried individuals did not differ significantly between the two groups ($\chi^2 = 0.03$, $p = 0.93$). The MDD group presented with a mean HDRS-17 score of 24.14 and a mean HAMA score of 20.09 (Table 1).

3.2 Spectral power and asymmetry analysis

Independent samples *t*-tests compared EEG relative band power across various brain regions between 86 MDD patients and 83 HCs. For the eyes-closed condition, MDD patients exhibited significantly higher beta2 band power in the RMFC, alpha band power in the RT,

and lower beta3 band power in the RMOC compared to HCs (Figure 1; Supplementary Table S1). Under the eyes-open condition, there was a significant increase in beta2 band power in the PFC, RMFC, LMFC, and CC in MDD patients, with a notable decrease in beta3 band power in the MOC relative to HCs. After FDR correction, beta2 band power in the PFC, RMFC, and LMFC in the MDD is still significantly increased, and the trend of other parameter characteristics remains unchanged but statistically significant diminished (Figure 2; Supplementary Table S1).

Asymmetry in alpha and beta1 band power between the RT and LT regions was more pronounced in MDD patients during the eyes-open condition, while the asymmetry in beta2 and beta3 band power was significantly less marked compared to HCs. Under the eyes-closed condition, the alpha band power asymmetry between RT and LT was significantly greater in MDD patients, whereas theta band power asymmetry was significantly reduced. After FDR correction, the statistically significant asymmetric differences between the two groups in beat2 band power at RT-LT in the eyes-open condition and in theta band power in the eyes-closed condition at RT-LT were attenuated, and all other parameters remained statistically significant (Table 2).

TABLE 1 Demographic and clinical characteristics of MDD and HC groups.

Characteristics	MDD	HC	Statistics	
	(n = 86)	(n = 83)	χ2/t	p value
Sex (male/female)	31/55	37/46	1.28	0.26
Age (years)†	26.16 ± 6.29	26.41 ± 8.24	−0.22	0.83
Education level (years) †	13.06 ± 3.15	12.84 ± 3.19	0.44	0.66
Married/Unmarried	57/28	54/28	0.03	0.93
HDRS-17†	24.14 ± 4.81			
HAMA†	20.09 ± 7.00			

†Mean ± SD; MDD, Major depressive disorder; HC, healthy control; HDRS-17, the 17-item Hamilton Depression Rating Scale; HAMA, the Hamilton Anxiety Scale-14.

3.3 Regression analysis of discrepant data

Binary logistic regression was utilized in 86 MDD patients and 83 HCs to identify potential EEG predictors of MDD, with the diagnosis as the dependent variable. EEG band powers showing significant differences in t-tests (beta2 in PFC, RMFC, LMFC, CC, beta3 in MOC for eyes-open; beta2 in RMFC, alpha in RT, beta3 in RMOC, RMFC, RT, MOC, LMOC for eyes-closed) and power asymmetries (alpha, beta1, beta2, beta3 between RT and LT for eyes-open; alpha, theta between RT and LT for eyes-closed) were included as independent variables. The analysis determined that beta2 band power in PFC with eyes open (B = 20.092, p = 0.011), beta3 in MOC with eyes open (B = −12.050, p < 0.001), beta2 in RMFC with eyes closed (B = 24.227, p < 0.001), asymmetry in beta1 band power between RT and LT with eyes open (B = 28.047, p = 0.018) and in alpha (B = 9.004, p = 0.013) and theta (B = −13.582, p = 0.008) with eyes closed were significant predictors of MDD (Table 3). The model's performance was validated using 10-fold cross-validation to ensure robustness. The average area under the ROC curve (AUC) from the cross-validation was approximately 0.7709, indicating a fair discrimination ability of the model. The sensitivity and specificity obtained were around 68.47 and 66.94%, respectively. To assess the statistical significance of the model's predictive capability, we calculated the 95% confidence interval for the AUC, which ranged from 0.7261 to 0.8592, not encompassing the null hypothesis value of 0.5 and thus confirming that the model performed significantly better than chance. The ROC curve was plotted to visually

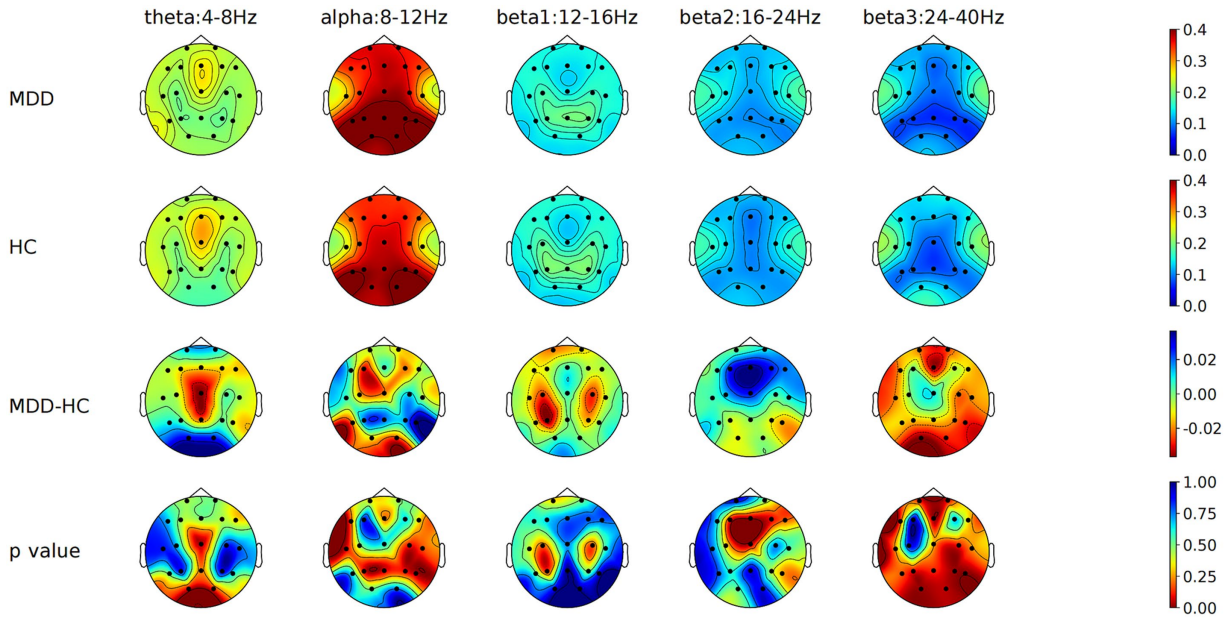

FIGURE 1
Comparison of relative power values of each frequency band in each brain region between MDD and HC groups with eyes closed. MDD, Major depressive disorder; HC, Healthy control; MDD-HC, Difference in relative power between two groups.

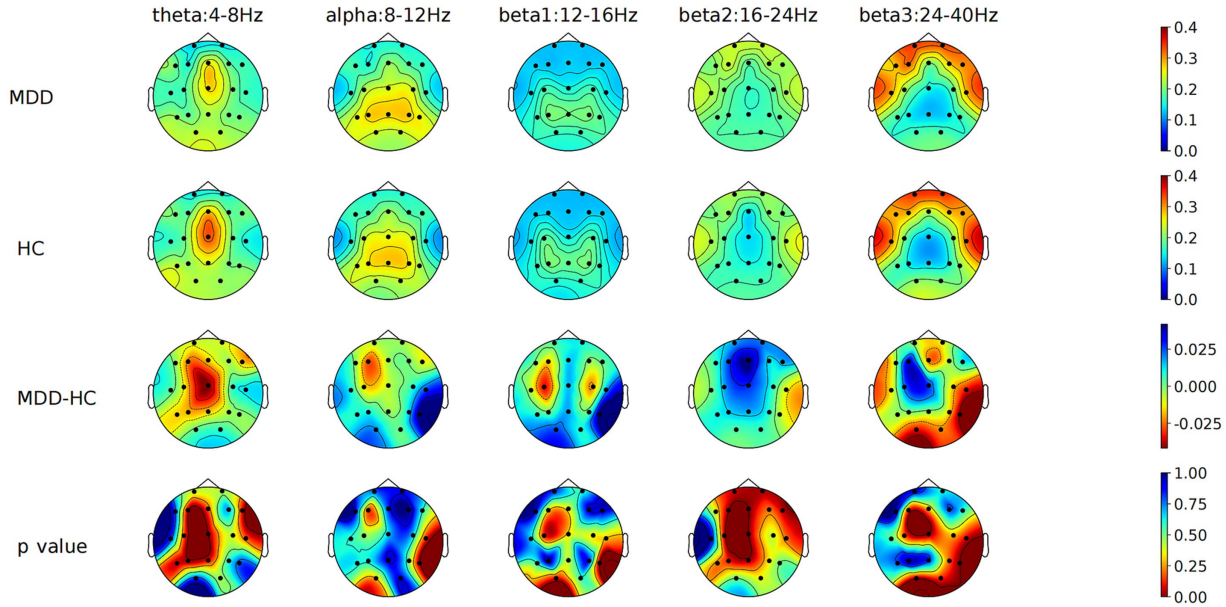

FIGURE 2
Comparison of relative power values of each frequency band in each brain region between MDD and HC groups with eyes open. MDD, Major depressive disorder; HC, Healthy control; MDD-HC, Difference in relative power between two groups.

TABLE 2 Comparison of relative power asymmetry between left and right brain regions in each frequency band in MDD and HC groups.

BR	FB	HC (EO)	MDD (EO)	Statistics (EO)			HC (EC)	MDD (EC)	Statistics (EC)		
		Mean ± SD	Mean ± SD	P1	P2	Effect Size (Cohen's d)	Mean ± SD	Mean ± SD	P1	P2	Effect Size (Cohen's d)
RMFC-LMFC	Theta	0.003 ± 0.043	0.005 ± 0.035	0.782	0.782	−0.043	0.003 ± 0.024	0.000 ± 0.018	0.377	0.505	0.148
	Alpha	0.002 ± 0.027	0.007 ± 0.025	0.189	0.27	−0.203	0.001 ± 0.025	0.000 ± 0.024	0.929	0.929	0.014
	Beta1	−0.001 ± 0.013	0.002 ± 0.014	0.21	0.21	−0.193	−0.002 ± 0.008	0.000 ± 0.009	0.361	0.472	−0.141
	Beta2	−0.002 ± 0.025	−0.003 ± 0.020	0.666	0.772	0.066	−0.001 ± 0.010	0.001 ± 0.013	0.353	0.353	−0.143
	Beta3	−0.003 ± 0.059	−0.012 ± 0.054	0.347	0.52	0.145	−0.001 ± 0.039	−0.002 ± 0.028	0.963	0.963	0.007
RMOC-LMOC	Theta	−0.007 ± 0.035	0.000 ± 0.023	0.141	0.423	−0.228	−0.003 ± 0.030	−0.004 ± 0.027	0.828	0.828	0.033
	Alpha	0.004 ± 0.025	0.000 ± 0.024	0.27	0.27	0.17	0.019 ± 0.043	0.009 ± 0.034	0.127	0.191	0.236
	Beta1	0.004 ± 0.014	0.001 ± 0.015	0.18	0.21	0.207	0.003 ± 0.017	0.005 ± 0.015	0.472	0.472	−0.111
	Beta2	−0.001 ± 0.014	−0.001 ± 0.012	0.772	0.772	0.045	−0.007 ± 0.017	−0.004 ± 0.014	0.227	0.34	−0.187
	Beta3	−0.001 ± 0.049	0.000 ± 0.032	0.799	0.799	−0.039	−0.013 ± 0.052	−0.006 ± 0.032	0.316	0.474	−0.155
RT-LT	Theta	−0.015 ± 0.045	−0.007 ± 0.053	0.339	0.509	−0.148	0.003 ± 0.024	0.000 ± 0.018	0.037	0.112	0.323
	Alpha	−0.010 ± 0.032	0.007 ± 0.041	0.004	0.012	−0.449	0.001 ± 0.025	0.003 ± 0.024	0.003	0.009	−0.463
	Beta1	−0.003 ± 0.018	0.008 ± 0.022	<0.001	0.001	−0.547	−0.002 ± 0.008	0.000 ± 0.009	0.283	0.472	−0.166
	Beta2	0.008 ± 0.033	−0.003 ± 0.033	0.037	0.111	0.324	−0.001 ± 0.010	0.001 ± 0.013	0.095	0.285	0.258
	Beta3	0.019 ± 0.055	−0.006 ± 0.071	0.013	0.038	0.388	−0.001 ± 0.039	−0.002 ± 0.028	0.222	0.474	0.188

MDD, Major depressive disorder; HC, healthy control; SD, standard error; EO, eyes open; EC, eyes closed; PFC, Prefrontal Cortex; RMFC, Right Medial Frontal Cortex; LMFC, Left Medial Frontal Cortex; LT, Left Temporal Cortex; RT, Right Temporal Cortex; RMOC, Right Medial Occipital Cortex; LMOC, Left Medial Occipital Cortex; P1, Uncorrected *p*-value; P2, FDR-corrected *p*-value.

represent the model's performance, with a blue line indicating the trade-off between sensitivity and specificity across different thresholds, and a grey dashed line representing the performance of a random classifier (Figure 3).

3.4 ROC curve analysis

ROC curve analysis in 86 MDD patients and 83 HCs evaluated the EEG band powers' predictive capabilities for MDD. The AUC

TABLE 3 Binary logistic regression of potential predictors of MDD.

State			*B*	SE	*p*
Eyes open	EEG relative band power	beta2 in PFC	20.092	7.872	0.011
		beta2 in RMFC	2.630	9.583	0.784
		beta2 in LMFC	−3.890	9.560	0.684
		beta2 in CC	−1.021	6.036	0.866
		beta3 in MOC	−12.050	3.078	<0.001
	Relative power asymmetry between left and right brain regions	alpha RT-LT	12.511	11.657	0.283
		beta1 RT-LT	28.047	11.859	0.018
		beta2 RT-LT	−0.514	9.718	0.958
		beta3 RT-LT	2.887	5.556	0.603
Eyes closed	EEG relative band power	beta3 in PFC	−2.030	3.188	0.524
		beta2 in RMFC	24.227	5.941	<0.001
		alpha in RT	1.070	2.172	0.622
		beta3 in RT	−4.128	4.113	0.316
		beta3 in MOC	10.822	10.618	0.308
		beta3 in RMOC	−3.355	7.857	0.669
		beta3 in LMOC	−16.962	10.146	0.095
	Relative power asymmetry between left and right brain regions	theta RT – LT	−13.582	5.119	0.008
		alpha RT – LT	9.004	3.640	0.013

PFC, Prefrontal Cortex; RMFC, Right Medial Frontal Cortex; LMFC, Left Medial Frontal Cortex; CC, Central Cortex; LT, Left Temporal Cortex; RT, Right Temporal Cortex; MOC, Medial Occipital Cortex; RMOC, Right Medial Occipital Cortex; LMOC, Left Medial Occipital Cortex.

indicated that beta2 band power in PFC with eyes open (AUC = 0.655, $p < 0.001$) could predict MDD with a sensitivity of 0.744 and specificity of 0.544, with an optimal cut-off point of 0.298 according to the Youden index. Similarly, the AUC for the asymmetry in beta1 band power between RT and LT with eyes open (AUC = 0.650, $p < 0.001$) predicted MDD with a sensitivity of 0.465 and specificity of 0.692, with an optimal cut-off of 0.308. For eyes-closed conditions, alpha (AUC = 0.590, $p = 0.002$) and theta (AUC = 0.639, $p = 0.04$) asymmetries between RT and LT were also predictive of MDD, with respective sensitivities of 0.279 and 0.523 and specificities of 0.892 and 0.723 at optimal cut-offs of 0.022 and 0.246.

3.5 Correlation analysis in MDD

Pearson correlation analysis explored the relationship between clinically relevant indicators and EEG band power in 86 MDD patients. Significant positive correlations emerged between HDRS-17 scores and beta2 band power in PFC ($r = 0.228$, $p = 0.035$), RMFC ($r = 0.240$, $p = 0.025$), and LMFC ($r = 0.223$, $p = 0.039$) with eyes open (Figure 4).

4 Discussion

In the present study, we investigated the alterations in EEG spectral power in individuals with MDD and explored their potential as objective markers for diagnosis and personalized treatment. Our findings revealed significant changes in beta2 activity in the prefrontal cortex, and alterations in beta3 power in the occipital cortex, alpha and beta power in the parietal and temporal regions. Binary logistic regression identified significant EEG predictors of MDD, including beta2 power in PFC with eyes open, beta3 power in MOC with eyes open, beta2 power in RMFC with eyes closed, asymmetry in beta1 power between RT and LT with eyes open, and asymmetry in alpha and theta power with eyes closed. The model's performance indicating fair discrimination ability. The ROC curve visually represented the model's performance, demonstrating its superiority over a random classifier. The regression model involving multiple variables demonstrates a better predictive ability for depression than any individual factor. Furthermore, the correlation between EEG spectral features and clinical indicators suggests the potential of EEG as a monitoring tool for the clinical course of MDD (Baskaran et al., 2012; Olbrich and Arns, 2013).

Spectral analysis revealed that individuals with MDD exhibited a marked elevation in beta2 relative band power in the PFC, RMFC, LMFC, and CC when their eyes were open. This augmentation in beta2 band power aligns with neurocognitive models of MDD, which suggest hyperactivity in specific brain circuits, correlating with rumination and negative cognitive biases—hallmarks of depression (Siegle et al., 2007). Such increased beta activity may mirror frontal lobe dysregulation, supporting the frontal lobe hypothesis of depression that associates changes in frontal brain activity with depressive symptoms (Pizzagalli, 2011; Sharpley et al., 2023b). Furthermore, Claverie et al. (2016) provide compelling evidence for the prognostic value of EEG spectral features, particularly beta2 main peak frequency, in identifying vulnerability to depression. This research, conducted on a rat model, demonstrates that individuals exhibiting lower beta2 main peak frequency prior to exposure to stressors were more likely to become vulnerable to depression, as indicated by persistent low serum BDNF levels. The persistence of altered EEG patterns in vulnerable animals across different time points—before stress exposure, immediately after, and one month later—suggests that these electrophysiological markers are stable indicators of susceptibility to depression.

Conversely, in the occipital region, particularly the MOC, the MDD group displayed a significant reduction in beta3 power, potentially indicating anomalies in visual processing or the occipital

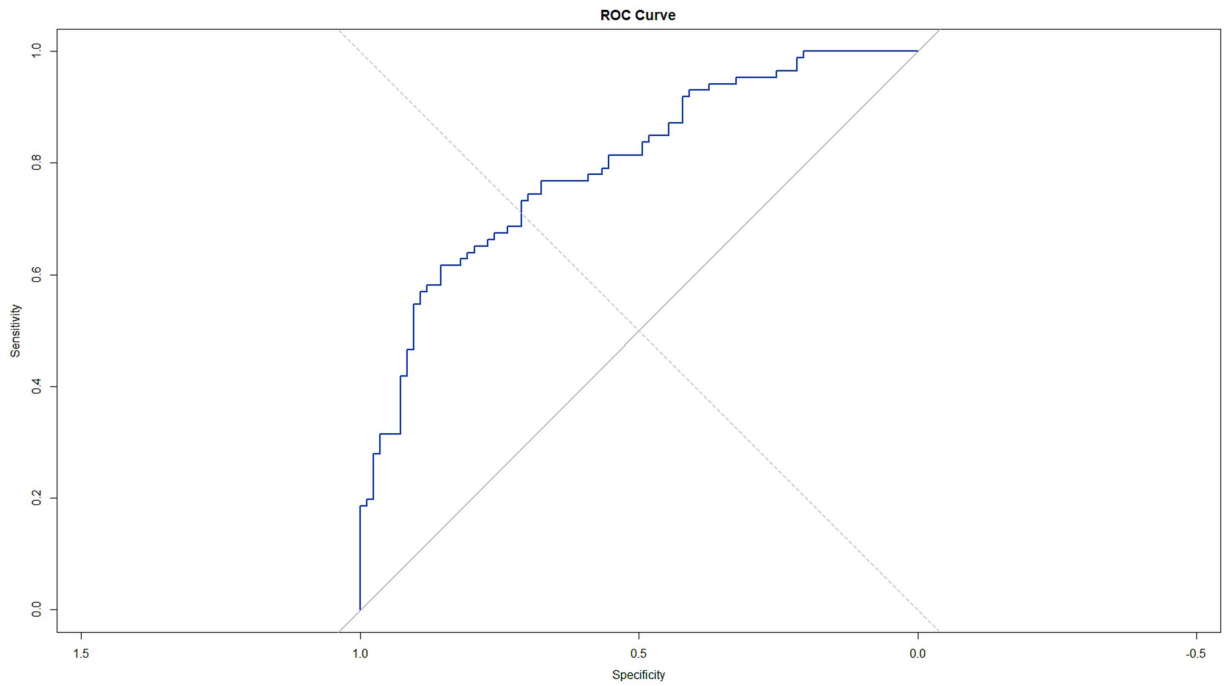

FIGURE 3
ROC curve analysis of the regression model in predicting Major depressive disorder.

lobe's role in mood regulation (Bruder et al., 2001; Liu et al., 2022). Our study's findings of altered band power in the parietal regions are corroborated by literature that implicates the parietal lobe in the neural circuitry of depression (Fales et al., 2008; Liu et al., 2023). The right parietal cortex, in particular, is associated with attentional control and emotional regulation—capabilities often compromised in MDD (Fales et al., 2008). Additionally, the parietal cortex's contribution to the default mode network (DMN), known to be disrupted in MDD, further supports our observations (Greicius et al., 2007; Sheline et al., 2009). The DMN is linked to self-referential mental activity, frequently exhibiting a negative bias in depression (Hamilton et al., 2012), which could manifest as altered EEG spectral power in the parietal regions.

Consistent reports of alpha band power alterations in the parietal regions suggest cortical hypoactivation in MDD (Pollock and Schneider, 1990; Bruder et al., 2001). Simultaneously, some studies propose that increased alpha power in the right parietal cortex reflects an internal attentional focus (Benedek et al., 2014) and a causal relationship between parietal alpha activity and spatial auditory attention (Deng et al., 2019). Our findings, consistent with these studies, propose that parietal hypoactivation may serve as a stable neurophysiological marker for MDD. Under the eyes-closed condition, our study identified an increase in alpha power in the RT region and alterations in beta3 power in the RMOC and LMOC among participants with MDD. These results are consistent with existing literature, which reports an increase in alpha band power during eyes-closed rest, potentially more pronounced in MDD (Thatcher, 2012; Chandler et al., 2022). The RT region, known for its role in emotional processing and memory—areas often compromised in MDD—may account for the specific regional increase in alpha power (Drevets, 1998; Bruder et al., 2001).

The power asymmetry between the LT and RT regions in the alpha and beta bands underscores the potential lateralization of brain activity in MDD (Messerotti Benvenuti et al., 2019). The beta3 power asymmetry between the RMOC and LMOC could reflect the lateralized dysfunction in MDD, which is believed to disrupt affective processing and attention (Bruder et al., 2001). Given the occipital cortex's primary role in visual processing, changes in beta3 power may indicate broader sensory processing issues in MDD (Kaiser et al., 2015). Moreover, these occipital lobe changes in beta3 power might relate to disruptions in the DMN, which includes occipital components and is affected in MDD (Greicius et al., 2007; Sheline et al., 2009). The DMN is associated with self-referential thought and mind-wandering, often negatively biased in MDD, which could be reflected in altered EEG patterns (Mayberg, 1997; Siegle et al., 2007). The observed imbalances may indicate disrupted interhemispheric communication, a factor implicated in the pathophysiology of depression (Uhlhaas and Singer, 2010). This lateralization has been noted in EEG studies, where alpha-band asymmetries correlated with emotional processing and depression severity (Bruder et al., 2001; Xie et al., 2023).

Furthermore, alterations in interhemispheric alpha power have been linked to functional disconnection between the cerebral hemispheres, potentially underlying the cognitive and affective disturbances in MDD (McVoy et al., 2019). Beta-band activity in the LT region is associated with language and executive functions, which are often impaired in MDD, suggesting that beta-band imbalances may correspond to the observed difficulties in cognitive control and verbal communication (Siegle et al., 2007; Pizzagalli, 2011). Additionally, research indicates that the LT region is involved in approach-related emotional processing, while the RT is associated with withdrawal-related emotions (Harmon-Jones et al., 2010). The alpha and beta power imbalance between these regions could reflect the emotional dysregulation and anhedonia commonly reported in MDD. Neuroimaging studies have supported the presence of structural and functional abnormalities in the temporal lobes of individuals with MDD, reinforcing the concept of lateralized

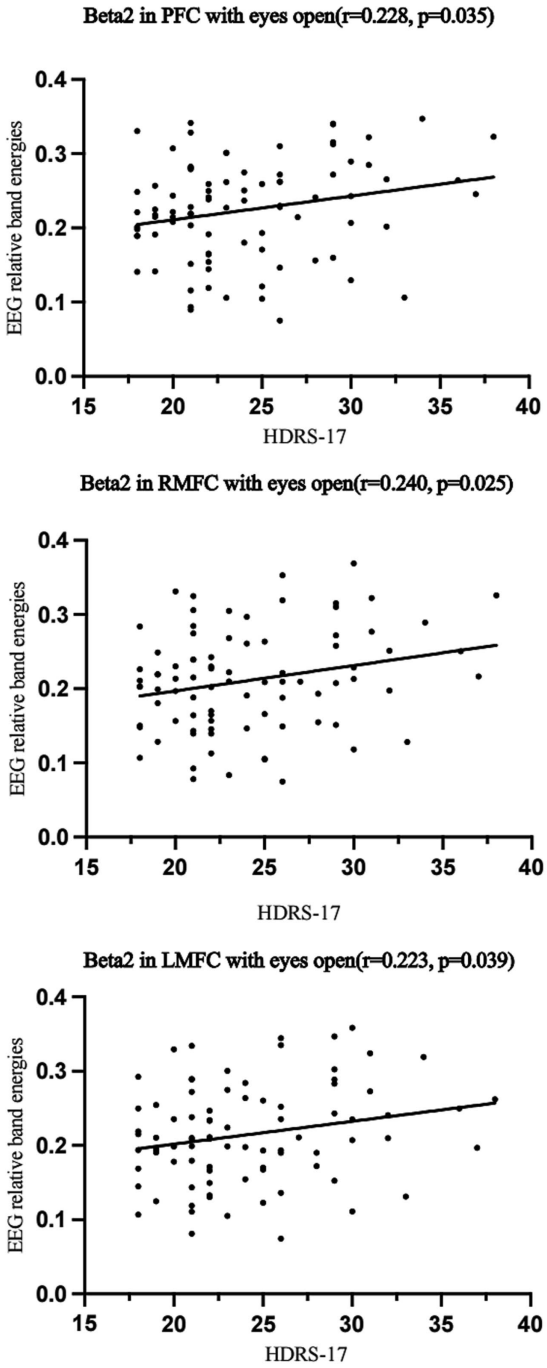

FIGURE 4
Pearson correlation analysis of EEG band power and asymmetry with HDRS-17 scores in patients with Major depressive disorder. MDD, Major depressive disorder; PFC, Prefrontal Cortex; RMFC, Right Medial Frontal Cortex; LMFC, Left Medial Frontal Cortex.

dysfunction (Drevets, 1998; Lai, 2014). These abnormalities may be connected to disrupted connectivity within the limbic–cortical networks, which is essential for emotional regulation and stress response (Mayberg, 1997; Sheline et al., 2009).

In our results, binary logistic regression analyses of EEG data have identified certain spectral power features as robust predictors of MDD. Notably, these features include the relative power of the beta2 band in the PFC with eyes open and asymmetries in the power of the beta1, alpha, and theta bands between the RT and LT regions, with eyes open and closed, respectively. The PFC is known for its role in executive functions and emotion regulation, both of which are often impaired in MDD (Siegle et al., 2007; Hiser and Koenigs, 2018). Beta2 activity, in particular, has been associated with active cognitive processes and attention (Engels et al., 2010), and its dysregulation may reflect the cognitive disturbances observed in individuals with MDD (Clark et al., 2017). When eyes are open, asymmetry in beta1 power between the RT and LT regions could indicate the lateralized processing of emotional stimuli and stress response, which are frequently disrupted in MDD. Asymmetries in alpha power, particularly with eyes closed, have been linked to altered arousal and vigilance states, which are characteristic features of MDD (Sharpley et al., 2023a). Furthermore, theta power is associated with memory and emotional processing, and its alteration may correspond to the memory deficits and negative bias in emotional processing characteristic of MDD (H. Jiang et al., 2022). These electrophysiological markers offer a window into the underlying neural mechanisms of MDD and may enhance the accuracy of diagnostic procedures when combined with traditional clinical evaluations (Pizzagalli, 2011; Jaworska and Protzner, 2013). By providing a quantitative measure of brain activity, EEG can offer a more nuanced understanding of the disorder (Baskaran et al., 2012; Olbrich and Brunovsky, 2021).

The analysis of the ROC curve for the predictive utility of single EEG spectral power in MDD resulted in modest Area Under the Curve (AUC) values, such as 0.655 for beta2 in the PFC with eyes open, indicating a fair level of discriminative ability. However, when multiple EEG spectral power and asymmetry were included in a binary logistic regression model, the average AUC improved to 0.7709, indicating a more robust discrimination ability. This variability highlights the complexity of MDD as a disorder and the challenges in identifying a single biomarker with high diagnostic accuracy (Insel et al., 2010). While the modest AUC values obtained from ROC curve analyses of EEG features in predicting MDD do not diminish the potential value of these measures, they emphasize the importance of a multimodal diagnostic approach that integrates EEG, clinical assessments, and other biomarkers. Previous studies have also indicated that composite EEG measurement indices, such as the Antidepressant Treatment Response Index (ATR), exhibit strong predictive accuracy in determining treatment response in MDD. For instance, retrospective analysis of an initial study involving subjects with MDD treated with selective serotonin reuptake inhibitors (SSRIs) or venlafaxine demonstrated that ATR predicted response with an accuracy of 70%, with 82% sensitivity and 54% specificity (Iosifescu et al., 2009). Furthermore, in the Biomarkers for Rapid Identification of Treatment Effectiveness in Major Depression (BRITE-MD) study, ATR showed predictive value by achieving an accuracy of 74% in predicting response and remission, with a sensitivity of 58%, specificity of 91%, positive predictive accuracy of 88%, and negative predictive accuracy of 67% (Leuchter et al., 2009). Our approach aligns with contemporary psychiatric practice, which emphasizes the integration of biological data to inform diagnosis and treatment response, ultimately aims to improve outcomes for individuals with MDD (Insel et al., 2010; Markiewcz, 2017).

Correlation analysis of EEG relative band power with clinical indicators in MDD patients has provided insightful data, revealing a significant positive relationship between HDRS-17 scores and increased beta2 activity in various frontal regions, including the PFC, with coefficients ranging from $r = 0.223$ to $r = 0.240$ (Koller-Schlaud et al., 2020). This suggests that as the severity of depression increases,

so does the beta2 activity in these areas. The positive correlation between HDRS-17 scores and increased beta2 activity in frontal regions suggests that EEG spectral features could serve as objective indicators for monitoring the clinical course of MDD.

However, this study is not without limitations. Given the relatively small sample size of our study, the sensitivity and specificity reported here may not accurately reflect what would be obtained in a larger, more heterogeneous population. Additionally, the cross-sectional nature of the study design precludes the ability to infer causality or the directionality of the observed relationships. Future research should include longitudinal designs to assess the temporal stability of EEG markers and their predictive value for treatment outcomes. While our findings provide valuable insights into EEG markers for MDD, they should be considered preliminary and warrant validation in larger-scale studies that can offer more definitive evidence of their generalizability. Moreover, the heterogeneity of MDD symptoms and the presence of comorbidities, such as anxiety disorders, may confound the EEG signals. Therefore, subsequent studies should consider stratifying participants based on symptom clusters or comorbid conditions (Frodl and O'Keane, 2013).

5 Conclusion

The study confirms the potential of multi-region EEG analysis in improving the diagnostic precision for MDD. MDD patients showed increased beta2 band power in the PFC, RMFC, LMFC, and CC under eyes-open conditions, and increased beta2 in RMFC and alpha in RT under eyes-closed conditions. Conversely, beta3 band power was lower in MDD across multiple regions. Notably, asymmetries in alpha and beta bands between right and left temporal cortices emerged as strong predictors of MDD. These EEG markers, along with clinical scores, provide potent diagnostic indicators for MDD.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Beijing Anding Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

XL: Writing – original draft, Writing – review & editing, Methodology, Supervision, Validation. HZ: Writing – original draft, Writing – review & editing, Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Validation. YC: Methodology, Software, Visualization, Writing – review & editing, Project administration, Supervision, Validation. TZ: Methodology, Software, Visualization, Writing – review & editing, Supervision, Validation. BW: Data curation, Software, Visualization, Writing – review & editing, Project administration, Resources. XX: Data curation, Methodology, Visualization, Writing – review & editing. SL: Data curation, Software, Validation, Visualization, Writing – review & editing. SS: Project administration, Resources, Validation, Visualization, Writing – review & editing. YY: Project administration, Resources, Writing – review & editing. XZ: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. LZ: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

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Conflict of interest

YC, TZ, and YY are employed by Gnosis Healthineer Co. Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2024.1362111/full#supplementary-material

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The neuroimmune pathway of high-altitude adaptation: influence of erythrocytes on attention networks through inflammation and the autonomic nervous system

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Introduction: Many studies have shown that the functional adaptation of immigrants to high-altitude is closely related to oxygen transport, inflammatory response and autonomic nervous system. However, it remains unclear how human attention changes in response to hypoxia-induced neurophysiological activity during high-altitude exposure.

Methods: In the present study, we analyzed the relationship between hypoxic-induced neurophysiological responses and attention networks in 116 immigrants (3,680 m) using an attention network test to simultaneously record electroencephalogram and electrocardiogram in combination with specific routine blood markers.

Results: Our analysis revealed that red blood cells exert an indirect influence on the three attention networks, mediated through inflammatory processes and heart rate variability.

Discussion: The present study provides experimental evidence for the role of a neuroimmune pathway in determining human attention performance at high- altitude. Our findings have implications for understanding the complex interactions between physiological and neurocognitive processes in immigrants adapting to hypoxic environments.

KEYWORDS

attention networks, neuroimmune, heart rate variability, red blood cell count, inflammation

1 Introduction

The oxygen scarcity and low-pressure conditions of high-altitude regions present unique physiological challenges to the inhabitants living in these regions. Among them, erythrocytes play a crucial role in adapting to the high-altitude environment. The body improves the efficiency of oxygen carrying and delivery by compensatory increase in the number of erythrocytes to maintain the normal function of tissues (Wood and Johansen, 1972; Raberin et al., 2022; Villafuerte et al., 2022). However, in recent years, it has been shown that such compensatory changes in red blood cells (RBCs) in immigrant populations living at high-altitude may not only involve the physiological aspects of oxygen transport, but also relate to cognitive functions such as attention (Xue et al., 2022).

The brain is the most oxygen-consuming organ in the human body (Raichle and Gusnard, 2002; Reichle, 2010; Yan, 2014), and hypoxia is a stressor of human beings (Virués-Ortega et al., 2004); thus, high-altitude hypoxia exposure would induce extensive effects on brain function (Chen et al., 2017, 2021; Zhang et al., 2018a,b; Xue et al., 2022). Previous studies have demonstrated that functional adaptations to high-altitude include multidimensional physiological and neurocognitive changes, such as efficiency of oxygen usage (Yan et al., 2010; Yan, 2014; Xue et al., 2022), inflammatory response (Caris and Santos, 2019; Nguyen et al., 2021), physiological homeostasis (Beall, 2007; Frisancho, 2013), brain morphology (Virués-Ortega et al., 2004; Yan et al., 2010), and cognitive performance (Ma et al., 2015; Taylor et al., 2015; McMorris et al., 2017; Zhang et al., 2018a, 2021; Chen et al., 2021). In human cognition, attention systems have been reported to be sensitive to hypoxia (Zhang et al., 2018a,b, 2021; Chen et al., 2021; Xue et al., 2022). High-altitude exposure leads to a generalized decrease in executive attention in immigrants. Longitudinal and controlled studies comparing high- and low-altitude adults have demonstrated effects on a variety of attentional domains, including alerting, orienting, and executive control. A 2-year follow-up study showed changes in executive control efficiency in high-elevation immigrants, but no significant changes in alerting or orienting networks (Xin et al., 2017). Similarly, an assessment of a 3-year cohort of immigrants showed a decrease in executive control efficiency relative to adults at lower altitudes (Zhang et al., 2021). Another study utilizing the Stroop task found a significant reduction in migrant accuracy and delayed response times after 2 years of exposure (Chen et al., 2021). However, it remains unclear how human attention changes with hypoxia-induced neurophysiological changes during prolonged hypoxic exposure. However, it remains unclear how human attention changes in response to hypoxia-induced neurophysiological activity during long-term hypoxia exposure.

Human behavior and cognition in high-altitude environments are tightly related to oxygen transport, the inflammatory response, and the autonomic nervous system (ANS) (Goodman et al., 2011; Trimmel, 2011; Omrani et al., 2017; Pun et al., 2019; Li et al., 2020). Exposure to high-altitude could increase inflammation, such as neutrophil count and the neutrophil/lymphocyte ratio (NLR), a reliable marker of chronic low-grade inflammation (Bhat et al., 2013; Lynall et al., 2019), which is associated with decreased executive attention function (Hou et al., 2022). The inflammatory response to oxygen metabolism is regulated by the ANS (Williams et al., 2019) and the properties of RBCs. The ANS plays an important role in the neurophysiological pathway responsible for adaptively regulating inflammatory processes (Williams et al., 2019), in which HRV is usually used as an index to depict the ANS (Zhang et al., 2014). Of note, HRV is generally considered a biomarker of top-down self-regulation (Holzman and Bridgett, 2017), reflecting the capacity of regulating cognitive activity, mood, and behavior in response to changing environmental demands (Porges, 2007; Thayer and Lane, 2009). The low frequency/high frequency (LF/HF) ratio is a sensitive indicator of HRV, and an increased LF/HF ratio indicates a lower HRV (Rombold-Bruehl et al., 2019). Many studies have shown that immediate exposure to high-altitude results in increased sympathetic activity followed by a significant increase in the LF/HF ratio (Bernardi et al., 1998; Kanai et al., 2001; Chen et al., 2008; Qian et al., 2020). In addition to the HRV change from high-altitude exposure, RBCs were compensatory increased in a hypoxic environment (Wood and Johansen, 1972; Raberin et al., 2022; Villafuerte et al., 2022), and RBCs are critical players in inflammation distinct from their function in oxygen transport (Lam et al., 2021; Xu et al., 2022). Together, HRV and RBCs are closely related to oxygen transport capacity, and both are associated with inflammatory responses; the complex interactions together determine the individual's physiological homeostasis (Taylor et al., 2010). Furthermore, the changed HRV and RBCs properties were observed to be associated with poorer external attention performance (Duschek et al., 2009; Williams et al., 2016).

To examine how the hypoxia-induced neurophysiological response (oxygen transport, inflammation and ANS) connects with human attention function during the long-term exposure, the current cross-sectional study employed ANT recording EEG and ECG simultaneously, also combining specific blood routine markers to examine the three distinct attentional processes (alerting, orienting, and executive control) in 116 immigrants who had been living in Tibet (3680 m) more than 3 years. Our primary analysis examined three neural markers of attention networks, and then we used mediation analyses to explore whether physiological indicators mediated the relationship between exposure and the attention network through a series of mediation analyses. Finally, we used a path model to explore the neurophysiological pathway by which erythrocytes influence the attention network through inflammation and HRV. To exclude the possible biases due to demographic, cultural, and socioeconomic differences, we controlled for sex, BMI, and age in assessing neuropsychological/attention differences. Studying this relationship in depth, we are expected to reveal the potential effects of erythrocyte changes on cognitive functions in high-altitude environments, providing new perspectives for understanding high-altitude adaptation. This will not only help to expand our knowledge of erythrocyte physiology in high-altitude environments but may also provide important clues for the prevention and treatment of related diseases and cognitive disorders.

Abbreviations: ANS, Autonomic Nervous System; ANT, Attention Network Test; BMI, Body Mass Index; ECG, Electrocardiograph; EEG, Electroencephalography; ERP, Event-Related Potential; HRV, Heart Rate Variability; ITC, Inter Trail Phase Coherence; LF/HF ratio, Low Frequency/High Frequency Ratio; LYMPH#, lymphocyte count; LYMPH%, lymphocyte percentage; NEUT#, neutrophilic granulocyte count; NEUT%, neutrophilic granulocyte percentage; NLR, Neutrophil to Lymphocyte Ratio; NG, normal group; RBC, Red Blood Cell count; RT, Response Time; SD, standard deviation.

2 Methods and materials

2.1 Study participants

We recruited 129 Han Chinese right-handed participants who had been working or living for more than 3 years in Lhasa (3680 m) for this study. All participants were born and raised in the central plain region of China (<1000 m), 1 subject withdrew from the

TABLE 1 Demographic information for participants.

Variables	Whole cohort ($N = 116$)
Age (mean, SD)	34.55 (3.45)
Sex (Male/Female)	55/61
BMI (mean, SD)	22.85 (3.44)
Education (%)	
High school graduate or below	11 (9.50%)
Junior college	17 (14.70%)
Undergraduate	44 (37.90%)
Postgraduate and above	44 (37.90%)

SD, standard deviation; BMI, body mass index.

physical examination due to fear of blood; 6 were excluded because of the quality of EEG data; 6 were excluded due to incomplete heart rate data. After excluding these data, statistical analysis was performed for the remaining 116 participants. None of the participants had neurological or mental illness, brain damage or drug addiction. All participants give written informed consent and are paid for their participation. The study was approved by the Ethics committee of Tibet University and follows the Declaration of Helsinki.

The average high-altitude exposure time of these participants (male: 55; female: 61) was 9.74 ± 3.61 years (range: 3-20 years), the average age was 34.55 ± 3.45 years (range: 27-41 years), and the average BMI was 22.85 ± 3.44 (range: 16.18-39.43). Their educational experiences fell into four categories: high school graduate or below, junior college, undergraduate, and postgraduate or above. Table 1 shows the demographic information of the participants in the study. And BMI, age, sex, and education levels were used as covariates in all our analyses.

2.2 Experimental procedures

At the beginning of the experiments, participants completed the demographic questionnaire, and the ANT experiment with EEG and ECG signals were recorded continuously with an ANT Neuro 64-electrode system and BioHarness Physiology Monitoring System, respectively. Then, the participants fasted overnight, and their serum samples were collected the next day at the Healthy Examination Center of Fukang (International) Hospital in Tibet (Figure 1).

2.3 Physiological measurements

Before the physicians' measurements, all the participants (116 samples) were previously introduced to administer the questionnaire and then the physical examination. The serum samples were drawn after overnight fasting for complete blood count measurement. The routine blood indices included red blood cell count (RBC counts, 10∧12/L), absolute neutrophil count (NEUT#), neutrophil percentage (NEUT%), lymphocyte percentage (LYMPH%), absolute lymphocyte count (LYMPH#, 10∧9/L), and neutrophil/lymphocyte ratio (NLR).

2.4 ECG data acquisition and analysis

ECG recordings were obtained by a BioHarness Physiology Monitoring System (Zephyr BioHarness data acquisition system with 2-lead configuration, BIOPAC Systems, Inc., 42 Aero Camio, Goleta, CA, USA) with MP 150 hardware and sampled at 1 kHz and AcqKnowledge 4.2.1 software. Two electrodes were connected to the chest and the second left rib. The grounding electrode GND was connected to the right abdomen after the skin was disinfected with alcohol. The ECG was zeroed online, with a 50 Hz main notch, 0.5 Hz high-pass filtering, and 35 Hz low-pass filtering. Raw ECG was filtered using a bandpass filter (2 to 40 Hz). HRV analysis of the RR tachogram was performed for frequency domain (by power spectral analysis using fast Fourier transformation) and time domain measures using the Kubios (version 4.2).

2.5 Attention network test

The ANT task was based on the version employed by Fan et al. (2007), which can effectively measure the efficiency of all three attentional network effects (i.e., alerting, orienting, and executive) by combining a cued reaction time task (Posner, 1980) with a flanker task (Eriksen and Eriksen, 1974). Notably, the ANT shows moderate to high reliability (Fan et al., 2002), including in adults exposed to high-altitude hypoxia (Zhang et al., 2018b, 2021).

Participants performed one practice block of 10 trials followed by 6 experimental blocks, and each block consisted of 108 trials. The participants saw a "target" row of 5 horizontally aligned images of arrows and had to indicate the direction of the central arrow, which faced either the same or the opposite direction as the four surrounding "flanker" arrows (Figure 2). The target rows appeared either below or above the center of the screen. In each trial, the target row was preceded by one of three different cue types: (1) no-cue; (2) an asterisk in the center of the screen (central-cue); (3) an asterisk either above or below the center of the screen (spatial-cue), which was always consistent with the spatial location of the subsequent target row. Each trial began with a 1000 ms fixation, and then a warning cue was presented for 200 ms. There was a short fixation period for a randomly variable duration (300 ms−1098 ms) after the cue, and then the target and flankers appeared simultaneously. The target and flankers were presented until the participant responded, but for no longer than 2000 ms. After participants made a response, the target and flankers disappeared immediately. After a 1000 ms interval, the next trial began. The fixation cross remained at the center of the screen during the whole trial (The experimental flow chart is shown in Figure 2).

The efficiency of each attention network was estimated by comparing the response times (RTs) to the target stimulus under different conditions (different types of cues and different types of flankers). Note that in these tasks, accuracy is usually near the ceiling, so analysis is not usually performed (Veríssimo et al., 2022). Specifically, the alerting network efficiency was measured as a center-cue relative to the benefits of the trial with no-cue (RT speed-up), the efficiency of the orienting network was measured for spatial-clues relative to the center-cues (RT speed-up), and

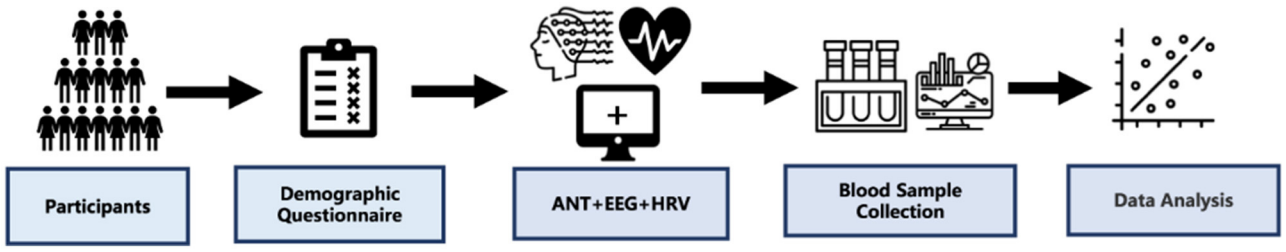

FIGURE 1
Study design. Participants completed the Demographic questionnaire, and we recorded the ANT experiment with EEG and ECG signals continuously. Then, the participants were fasted overnight, and their blood samples were collected at the next day.

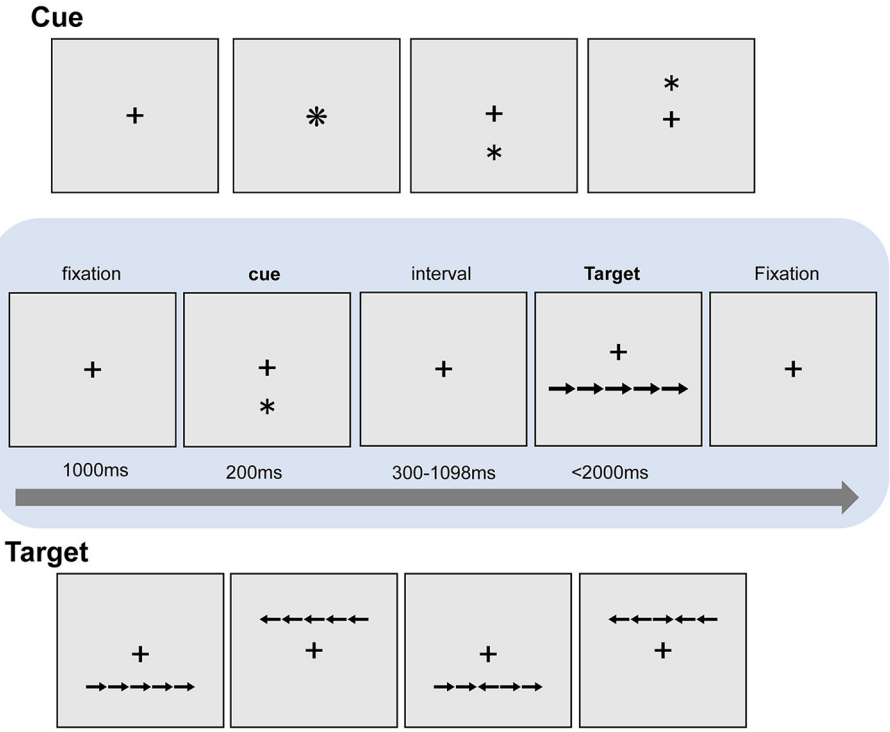

FIGURE 2
The ANT paradigm. A trial begins with a 1000 ms fixation period, and then a warning cue is presented for 200 ms. There is a short fixation period for a randomly variable duration after the warning cue, and then the target and flankers appear simultaneously. The target and flankers were presented until the participant responds, but for no longer than 2000 ms.

the benefits efficiency of the executive network was measured for incongruent flanks relative to the congruent flankers (the cost of RT deceleration); that is, the greater the interference caused by the flankers pointing in the opposite direction, the lower the efficiency of the executive network.

2.6 EEG recording and preprocessing

Continuous EEG was recorded at a sampling frequency of 1000 Hz by an ANT Neuro 64-electrode system (https://www.ant-neuro.com). Electrodes were positioned using the standard 10-20 system, and all impedances were kept below 5kΩ. The online reference electrode was placed on CPz, and the ground electrode was placed on FCz. Data processing and analyses were performed using the MATLAB toolbox EEGLAB (Delorme and Makeig, 2004) and Fieldtrip (Oostenveld et al., 2011) in MATLAB (version 2013b, The MathWorks). Raw data were downsampled to one-fourth (256 Hz) of the original sample rate before processing. Continuous EEG data were rereferenced offline to the average of all scalp electrodes, high-pass filtered at 0.1 Hz, and low-pass filtered below 40 Hz using a Basic FIR filter. For stimulus-locked analyses, the critical epochs ranged from −500 ms to 1000 ms relative to the onset of the stimulus, with −500 ms to 0 ms serving as the baseline. To remove ocular and muscle artifacts (including eye movements, blinks, heartbeat, and muscle artifacts), independent component analysis (ICA) was performed using the EEGLAB toolbox (on average, five components per participant were removed, SD = 2.0). Any remaining trials in which the amplitude exceeded ±100 μV were rejected. ERPs were computed

by taking the average of all baseline-corrected trials (200 ms relative to stimulus onset) for each condition combined across the six experimental blocks. Amplitudes of P300 waves under target conditions were assessed by averaging single-trial amplitude values across time windows.

Time-frequency representations of the cleaned and epoched data were estimated per-trial using a 0.5 s Hanning taper applied in steps of 20 ms from −0.3 s to 0.8 s relative to stimulus onset (implemented in the Fieldtrip Toolbox, ft_freqanalysis function with the mtmconvol method). Frequencies ranged between 2 Hz and 40 Hz with a resolution of 2 Hz. We measured the absolute difference in oscillatory power in the alpha and theta bands among the no-cue, spatial-cue and center-cue conditions because the ANT test provided a very limited baseline period, i.e., the pre-cue interval (Balter et al., 2019).

For the "alerting" and "orienting" efficiency, we focused on alpha power (averaged across 8 Hz−14 Hz) and theta power (averaged across 4 Hz−8 Hz) in the interval between 100 ms post-cue onset to 300ms for center cues minus no cues (alerting) and spatial cues minus center cues (orienting). The regions of interest (ROIs) included the posterior channels for P3, P4, and Pz and the occipital channels for O1, O2, and Oz. For the "executive" efficiency, we examined the post-target differences in theta power (averaged across 4 Hz−8 Hz) between incongruent target flankers and congruent target flankers in the interval 300 ms−700 ms post-target onset. The ROIs included the frontal central channels for Fz, FCz, and Cz.

We computed the intertrial phase coherence from the Fourier representation using the following formula:

$$ITC\left(f\right) = \frac{1}{n}\sum_{i=1}^{n}\frac{Z_i(f)}{|Z_i\left(f\right)|}$$

Phase coherence for the no-cue condition was subtracted from each center-cue condition, the center-cue was subtracted from each spatial-cue condition, and the congruent criteria were subtracted from the incongruent condition. The resulting difference was utilized in the statistical analysis as the phase coherence of alerting, orienting, and executive, respectively.

ITC measured the temporal consistency of the phase value for a given frequency band at a certain time point. Phase coherence varies from 0 to 1, where 0 indicated absence of any EEG phase consistency across trials, and 1 indicated identical EEG phase consistency across trials (Delorme and Makeig, 2004).

2.7 Cognitive data calculation and analysis

Trials with incorrect responses and RTs that were not within the scope (mean ± 3 SD) were excluded from each participant. The network score was calculated according to the three operational definitions of network effects.

2.7.1 Methods of behavior calculation

The efficiency of three attentional network scores based on the RTs was calculated as follows:

Alerting effect = RT_{no-cue} - $RT_{center-cue}$

Orienting effect = $RT_{center-cue}$ - $RT_{spatial-cue}$

Conflict effect = $RT_{incongruent}$ - $RT_{congruent}$.

2.7.2 Methods of EEG calculation

The contrasts for the alerting and orienting effects were reversed in the time domain, frequency domain, and time-frequency properties (i.e., alerting effect = center-cue - no-cue, orienting effect =spatial-cue - center-cue), and the contrasts for the executive control effect were the same as those for behavior (i.e., executive control effect = incongruent - congruent) (Fan et al., 2007).

2.8 Mediation analysis

Path modeling is a more flexible and powerful extension to the regression model where directional hypotheses about linear relationships between independent variables (RBCs) and dependent variables can be tested (three attention networks). It should be noted that path modeling does not provide evidence for the causality of such relationships. However, it may indicate whether the causal model under investigation is compatible with the data. The analyses were performed using online SPSS analysis software -SPSSAU.

All hypothesis tests conducted were two-tailed. We reported X^2 fit statistics, RMSEA with its 90% CI and SRMR. RMSEA of <0.05 and an SRMR below 0.1 imply a good fit. We also reported the CFI and the TLI, where values of CFI and TLI over 0.95 represented good fit. For model comparisons, we reported the robust (scaled) Satorra-Bentler X^2 difference test. We also reported the BIC, which is penalized for the number of freely estimated parameters, favoring the least complex model. As a rule of thumb, a BIC difference over 10 is considered very strong evidence against the model with the highest BIC, 6 to 10 are considered strong evidence, 2 to 6 are considered positive evidence, and 0 to 2 are considered negligible evidence.

3 Results

3.1 Neurophysiological effect of hypoxic exposure on attention

To examine the neurophysiological effect of hypoxic exposure on attention, we first sought to identify, a priori, key neural signatures that underlie the attention network in adults with hypoxic exposure. The results showed that the alerting efficiency was positively correlated with the parietal and occipital theta band (4 Hz−8 Hz) power (Figure 3A) in the interval 150 ms−300 ms post-cue onset for center cues vs. no cues (Pearson's correlation: $r = 0.205$, $P = 0.024$) (Figure 3B); orienting efficiency showed a significantly positive correlation to orienting alpha ITC (Parietal and occipital alpha (8 Hz−14 Hz) (Figure 3C) intertrial coherence in the interval 150 ms−250 ms post-cue onset for spatial cues vs. center cues) (Pearson's correlation: $r = 0.210$, $P = 0.023$) (Figure 3D); and executive efficiency showed a significantly

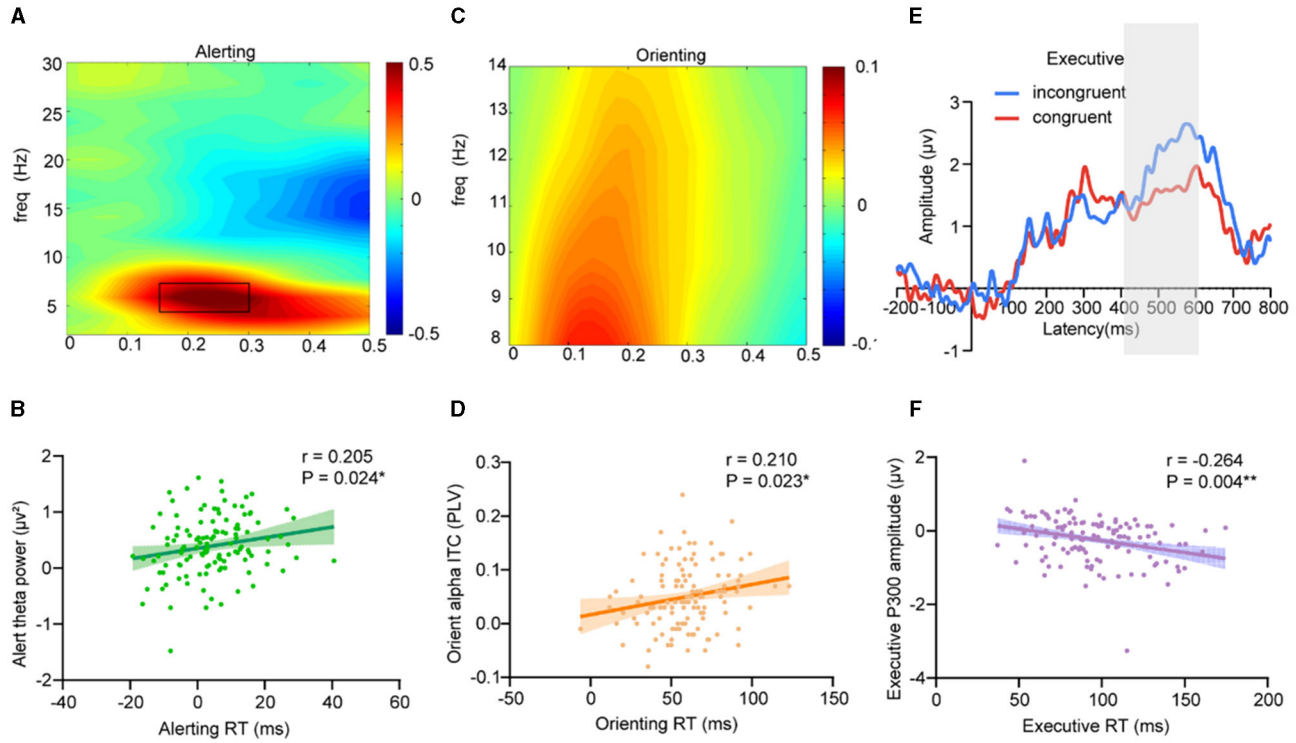

FIGURE 3
Neural markers of attention network performance. **(A, B)** Alerting efficiency showed a significantly positive correlation to the parietal and occipital alpha band (8 Hz−14 Hz) power in the interval 150 ms−300 ms post-cue onset for center cues vs. no cues (Pearson's correlation: $r = 0.205$, $P = 0.024$); **(C, D)** Orienting efficiency showed a significantly positive correlation to orienting alpha ITC (Parietal and occipital alpha (8 Hz−14 Hz) inter-trial coherence in the interval 150 ms−250 ms post-cue onset for spatial cues vs. center cues) (Pearson's correlation: $r = 0.210$, $P = 0.023$); **(E, F)** Executive efficiency showed a significantly negative correlation to P300 amplitude (400 ms−600 ms) (Pearson's correlation: $r = -0.264$, $P = 0.004$).

negative correlation to P300 amplitude (Figure 3E) (Pearson's correlation: $r = -0.264$, $P = 0.004$) (Figure 3F).

3.2 Relationships between neurophysiological indicators and behavioral performance

We calculated the partial Pearson's correlation coefficient to estimate the relationship between neurophysiological indicators and behavioral performance, controlled BMI, age, sex, and education (Figure 4). The results showed that RBCs was significantly positively correlated with NLR ($r = 0.244$, $P = 0.010$), NLR was significantly negatively correlated with LF/HF ($r = -0.215$, $P = 0.023$), and LF/HF was significantly correlated with executive RT ($r = 0.214$, $P = 0.024$), Alert theta power ($r = -0.239$, $p = 0.011$) and Orient alpha ITC ($r = -0.193$, $P = 0.042$).

3.3 Mediation pathway model between RBCs and the attention network

To examine the effect of oxygen transport capacity (i.e., RBC count) on the attention network, we used path modeling to examine whether RBC count was related to three attention networks through the inflammatory markers NLR and HRV. The mediation pathway analyses showed that RBC count was related to higher NLR (Effect = 0.399, S.E. = 0.147, $z = 2.71$, Pearson's effect size $r = 0.359$, $P = 0.007$) but not the LF/HF ratio (Effect = 0.094, S.E. = 0.247, $z = 0.379$, $r = 0.035$, $P = 0.704$) or the three attention networks for alerting (Effect = 0.135, S.E. = 0.127, $z = 1.064$, $r = 0.143$, $P = 0.287$), orienting (Effect = −0.01, S.E. = 0.014, $z = -0.736$, $r = -0.099$, $P = 0.462$) or executive control (Effect = 0.003, S.E. = 0.007, $z = 0.505$, $r = 0.067$, $P = 0.614$). The NLR was related to the LF/HF ratio (Effect = −0.504, S.E. = 0.213, $z = -2.373$, $r = -0.211$, $P = 0.018$) but not related to the three attention networks for alerting (Effect = 0.137, S.E. = 0.079, $z = 1.728$, $r = 0.162$, $P = 0.084$), orienting (Effect = −0.009, S.E. = 0.009, $z = -1.027$, $r = -0.096$, $P = 0.305$), or executive control (Effect = −0.002, S.E. = 0.004, z =-0.539, $r = -0.05$, $P = 0.59$). The LF/HF ratio was related to three attention networks for alerting (Effect = −0.067, S.E. = 0.033, $z = -2.052$, $r = -0.191$, $P = 0.04$), orienting (Effect = −0.009, S.E. = 0.004, $z = -2.452$, $r = -0.228$, $P = 0.014$), and executive control (Effect = 0.004, S.E. = 0.002, $z = 2.284$, $r = 0.209$, $P = 0.022$). The model fit was excellent (Figure 5 and Table 2).

We report chi-square (X^2) fit statistics, the root mean squared error of approximation (RMSEA), standardized root mean square residual (SRMR), the comparative fit index (CFI), the Tucker–Lewis index (TLI), and the Bayesian information criterion (BIC) (see "Materials and Methods"). Robust fit statistics indicated a good fit for the model with both predictors ($X_2^2 = 2.617$, $P = 0.106$, CFI

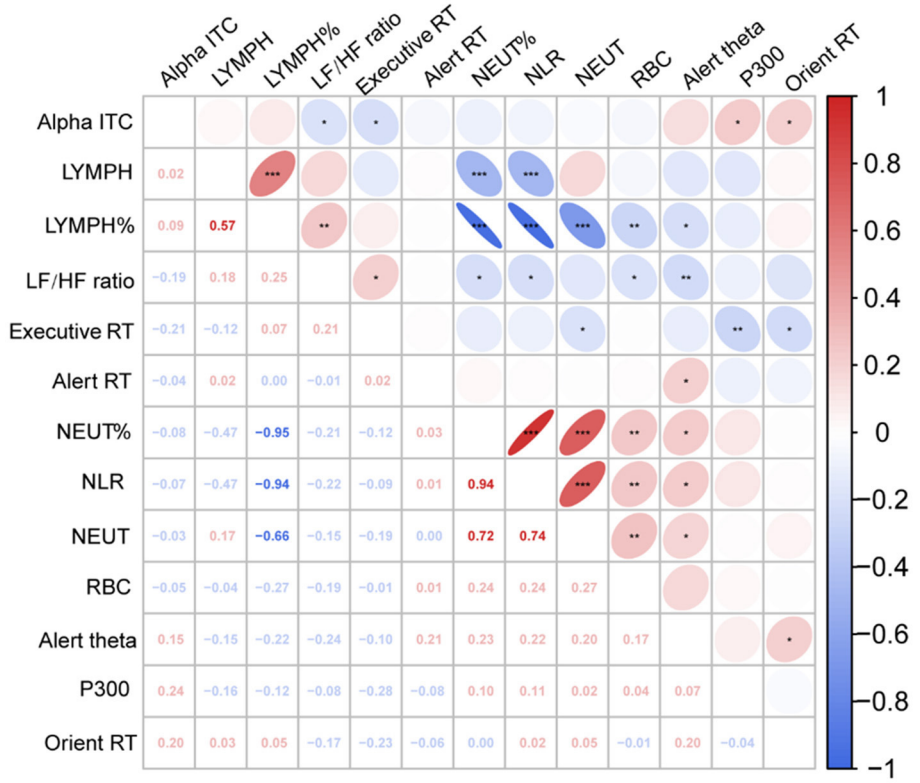

FIGURE 4
Partial correlation heat map among study variables. Executive RT, Executive response time; Alert RT, Alert response time; Orien RT, Orient response time; Alpha ITC, Orient alpha inter trail phase coherence; LF/HF Ratio, low frequency/high frequency ratio; RBC, red blood cell count; NLR, neutrophil-to-lymphocyte ratio; NEUT, neutrophilic granulocyte count; NEUT%, neutrophilic granulocyte percentage; LYMPH, lymphocyte count; LYMPH%, lymphocyte percentage.*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

= 0.998, TLI = 0.916, RMSEA = 0.119, 90% CI = 0.106 to 0.303, SRMR = 0.014).

4 Discussion

In this study, ANT was used in combination with EEG, ECG, and blood routine indicators to explore the relationship between hypoxic-induced neurophysiological response and attentional function of Tibetan immigrants. We first identify, a priori, key neural markers that underlie the attention network in Tibetan immigrants. Furthermore, we explored the effect of oxygen carrying on attention networks, and pathway analysis showed that the RBCs as oxygen carrying cells affected the three attention networks through inflammation and HRV. All these observations provide experimental evidence for the existence of a neuroimmune pathway rooted in RBCs, which represents oxygen transport capacity and is the basic physiological mechanism that determining human attention performance in a high-altitude environment.

RBCs, as oxygen-carrying cells, indirectly affected the three attention networks. Inflammation and HRV mediate this relationship. Given that HRV and inflammatory markers are important indicators of center-peripheral integration and homeostasis (Taylor et al., 2010), we believe that the key to the influence of RBCs on the attention network of immigrants may be to improve the oxygen transport capacity and maintain homeostasis by increasing RBCs within the normal range. Blood consists of 80% RBCs, especially hemoglobin, which carries oxygen to maintain brain functions. RBCs also play an important role in inflammation and the immune system (Lam et al., 2021; Xu et al., 2022). Our previous study also found that RBCs not only triggered internal-sensory representation of the insula association of orienting but also induced immune responses corresponding to executive control (Xue et al., 2022). Interoceptive inference (that is, the approximate Bayesian inference about the state of the internal) can be used to explain how organisms regulate homeostasis in hypoxic environments by making decisions about external perception and proprioception, in which the insular cortex plays a key role (Seth, 2013; Gu and FitzGerald, 2014). In a hypoxic environment, the brain senses hypoxia externally, increasing the oxygen-carrying capacity of RBCs as compensation (Wood and Johansen, 1972; Raberin et al., 2022; Villafuerte et al., 2022), and then the internal environment of the body is homogenized and controlled by autonomic reaction. When the brain perceives the gap between external perception and proprioception, it makes decisions through interoceptive inference, which is the basis of behavioral response (Gu and FitzGerald, 2014).

HRV may be the key to regulating the relationship between oxygen transport capacity and attention networks. The response of the autonomic nervous system (ANS) is the key to acclimation

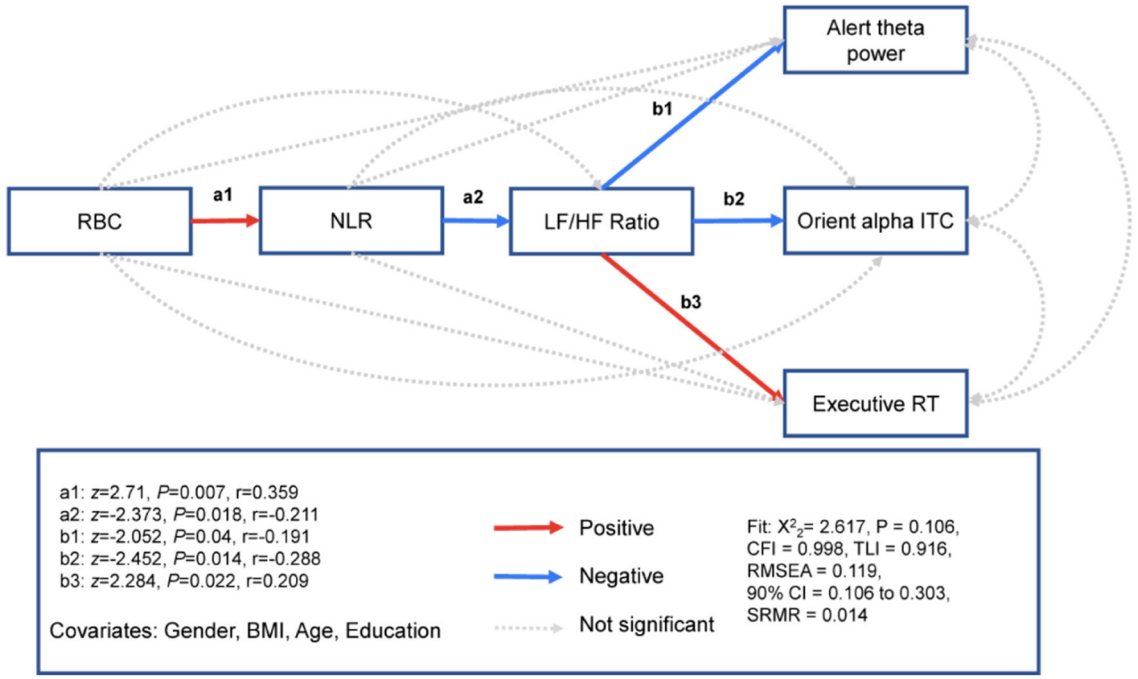

FIGURE 5
RBC associated with three attention networks, respectively. Path model showing that RBC specificity is associated with the neurophysiological markers of alerting, parietooccipital theta power; the neurophysiological markers of orienting, parietooccipital alpha ITC; and executive RT through inflammation and HRV. z, standardized path coefficient; r, Pearson's r effect size. $N = 116$.

during high-altitude exposure, which were often evaluated by HRV (Zhang et al., 2014; Temme et al., 2023). High-altitude exposure is an effective activator of the ANS (Roche et al., 2002; Taralov et al., 2018; Temme et al., 2023), resulting in decreased parasympathetic tone and increased sympathetic tone, and decreased HRV. HRV as one of the robust resilience markers (Walker et al., 2017) indicates the activity of the vagus nerve (i.e., primary parasympathetic nerve), which reflects the influence of the parasympathetic nervous system (PNS) on cardiac regulation (Laborde et al., 2017). Higher HRV physiologically indicates lower stress, higher ability to cope with stress, appropriate adaptation and flexibility to environmental changes, and more effective self-regulation (Shaffer and Ginsberg, 2017; Christodoulou et al., 2020). HRV can also predict the outcome of cognitive tests representing executive function. The neurovisceral integration model (NIM) view suggests that the subfrontal inhibitory circuit is connected to the heart via the vagus nerve, which provides inhibitory input to the heart, and that the prefrontal cortex (PFC) is also associated with the inhibitory capacity of executive function (Thayer et al., 2009). Furthermore, based on consistent evidence from many studies, a decrease in cardiac parasympathetic activity has been reported in both rat and human studies because of high-altitude exposure (Siebenmann et al., 2017; Beltrán et al., 2020).

Furthermore, the complex combination of physiological, behavioral, emotional, and cognitive processes involved in self-regulation and adaptation may have a common basis in that HRV will be linked to all these various forms of regulation (Holzman and Bridgett, 2017). HRV plays a key role in homeostasis, and there is evidence that the parasympathetic branch of the autonomic nervous system (ANS) plays a particularly critical role in modulating inflammation (Borovikova et al., 2000). Specifically, the parasympathetic nervous system (PNS) is involved in monitoring current levels of inflammation and reducing the production of inflammatory cytokines through rapid afferent and efferent signals from the vagus nerve (Tracey, 2002). LF/HF ratio is a sensitive index of HRV at high-altitude (Zhang et al., 2014), is an indicator of sympathetic vagus nerve balance or a reflection of sympathetic nerve regulation (Heathers, 2014). Elevated LF/HF ratios may indicate ANS dysfunction, leading to sympathetic vagus imbalance and sympathetic overweight (Kuriyama et al., 2010; Chen et al., 2011). HRV reflects the regulatory function of ANS and the brain's control over behavior and peripheral physiology and is a good biomarker of individual adaptation (Zhang et al., 2014). The degree of inflammatory response is important because an extreme or inadequate response can cause varying degrees of harm to an individual (Williams et al., 2019). In our results, the overall NLR range was <3. Here, it should be carefully explained that the increase of RBCs is accompanied by the increase of NLR. Some studies have shown that NLR <3 belongs to the normal range (Bahrami et al., 2019).

We also observed the effects of demographic variables on the attention network and immune system of immigrants. Specifically, we observed that gender was significant in the prediction of LF/HF ratios and NLR, while BMI also showed significance in the prediction of Executive RT. The effect of gender may reflect biological differences in neuropsychological functioning and immune system regulation. Previous studies have suggested

TABLE 2 Inflammation, HRV, and demographic variables as predictors for the effect of RBCs on three attention networks.

Outcome	Predictor	Effect	s.e.	z	*P* (>|z|)	r
Alert theta power	RBC	0.135	0.127	1.064	0.287	0.143
	NLR	0.137	0.079	1.728	0.084	0.162
	LF/HF Ratio	−0.067	0.033	−2.052	**0.04**	**−0.191**
	Gender	0.061	0.138	0.441	0.659	0.058
	Age	−0.006	0.014	−0.407	0.684	−0.037
	BMI	−0.005	0.015	−0.327	0.744	−0.031
	Education	0.067	0.052	1.289	0.198	0.12
Orient alpha ITC	RBC	−0.01	0.014	−0.736	0.462	−0.099
	NLR	−0.009	0.009	−1.027	0.305	−0.096
	LF/HF Ratio	−0.009	0.004	−2.452	**0.014**	**−0.228**
	Gender	0.008	0.015	0.505	0.613	0.066
	Age	−0.001	0.002	−0.328	0.743	−0.03
	BMI	0.001	0.002	0.331	0.74	0.032
	Education	−0.006	0.006	−1.072	0.284	−0.1
Executive RT	RBC	0.003	0.007	0.505	0.614	0.067
	NLR	−0.002	0.004	−0.539	0.59	−0.05
	LF/HF Ratio	0.004	0.002	2.284	**0.022**	**0.209**
	Gender	−0.002	0.007	−0.206	0.837	−0.026
	Age	0.001	0.001	1.583	0.113	0.144
	BMI	0.002	0.001	1.961	**0.05**	**0.184**
	Education	−0.002	0.003	−0.72	0.471	−0.066
NLR	RBC	0.399	0.147	2.71	**0.007**	**0.359**
	Gender	0.339	0.161	2.111	**0.035**	**0.271**
	Age	0.018	0.017	1.056	0.291	0.098
	BMI	−0.006	0.018	−0.343	0.731	−0.033
	Education	−0.056	0.062	−0.904	0.366	−0.085
LF/HF Ratio	NLR	−0.504	0.213	−2.373	**0.018**	**−0.211**
	Gender	−0.651	0.271	−2.407	**0.016**	**−0.217**
	Age	−0.025	0.04	−0.639	0.523	−0.059
	BMI	0.003	0.04	0.071	0.943	0.007
	Education	−0.035	0.146	−0.24	0.81	−0.022
Orient alpha ITC	Alert theta power	0.004	0.003	1.458	0.145	0.123
Alert theta power	Executive RT	−0.001	0.001	−0.586	0.558	−0.048
Executive RT	Orient alpha ITC	−0.000	0.000	−1.949	0.051	−0.164

N = 116. Significant paths are emboldened. Robust model fit indices: $X^2 = 2.617$, P = 0.106, CFI = 0.998, TLI = 0.916, RMSEA = 0.119, 90% CI = 0.106 to 0.303, SRMR = 0.014. BMI, body mass index; Orienting alpha ITC, orienting alpha inter trail phase coherence; LF/HF Ratio, low frequency/high frequency ratio; RBC, red blood cell count; NLR, neutrophil-to-lymphocyte ratio; Effect, unstandardized path coefficient; s.e., robust standard error; z, standardized path coefficient; r, Pearson's r effect size; 95% CI, 95% confidence interval of the effect size.

that gender may play a key role in the interactions between the autonomic nervous system and the immune system (Ferguson et al., 2013; Fransen et al., 2017), which in turn affects the LF/HF ratio and the NLR. Further studies could explore the underlying mechanisms of these gender differences to better understand the effects of these variables on attentional networks and immune indexes. And the significance of BMI in the prediction of Executive RT may reflect the complex relationship between BMI and executive function. Several studies have suggested that changes in BMI may be associated with adjustments in executive function (Stanek et al., 2013; Mac Giollabhui et al., 2020), and our findings emphasize the importance of this association. Overall, the significant effects of these demographic variables provide the impetus for further research to delve into the physiological basis of the relationship between gender and BMI and the attentional network and immune system. It also highlights the importance

of the need to consider these factors in more detail in future studies to better understand the role of individual differences in the neuroimmune regulation of immigrants.

Our results confirm the theory of the neurovisceral integration model (NIM) in high-altitude. According to Thayer and Lane (2000) on neuro-visceral integration (Thayer et al., 2009; Park and Thayer, 2014), the strong vagal regulation of the heart is related to the effective function of self-regulating neural circuits, which enable the body to respond quickly and flexibly to various environmental demands. Our results suggest that HRV (LF/HF ratio) can predict performance of executive control behavior, as well as brain activity during alerting and orienting. It is worth noting that the theta power represents the cognitive resources related to attention (Thayer and Lane, 2000; Thayer et al., 2009; Park and Thayer, 2014), alpha ITC represents the selective inhibition of target information in sensory input (inhibition of irrelevant information and discrete cognitive processes) (Hanslmayr et al., 2005; Busch et al., 2009; Gutteling et al., 2022), P3 may be a neurophysiological marker sensitive to high-altitude exposure (Wesensten et al., 1993; Singh et al., 2004; Wang et al., 2021). P3 amplitude reflects the allocation of attentional resources (Polich, 2007; Fogarty et al., 2018), and a decrease in amplitude indicates a reduction in the remaining effective indicator of mental resources (Magliero et al., 1984; Clayson and Larson, 2011; Schmidt-Kassow et al., 2013; Fogarty et al., 2018).These also indicate that immigrants with better oxygen transport ability have more cognitive resources in attention activities and better selective inhibition of target information, which is realized through the regulation of the autonomic nervous system on the homeostasis of the organism. Previous studies also found that cardiac vagus nerve (CVN) activity is associated with early attention orienting and promotes flexible absorption of effective orientation information (Sørensen et al., 2019). These results suggest that RBCs in high-altitude immigrants is associated with better cardiac vagal tone, which is related to the effective function of attentional self-regulating neural circuits, increasing cognitive resources in the process of selective attention, and improving the selective attention ability to target information.

Limitations of this study and several problems need to be considered in the future work. First, the results of this study need to be further verified and extended, for example (1) to test other aspects of cognitive function; (2) Study individual differences in cognitive function caused by exposure; Secondly, the present study only identified a neuroimmune pathway of RBCs affecting attention function in high-altitude immigrants, and we do not know whether this pathway is also present in low-altitude populations or in age- and gender-matched indigenous Tibetan residents, and future studies could give the results of differences in the study variables between the indigenous Tibetan residents and immigrant populations and enrich the results of the possible adaptive differences. (3) We did not consider the factors that influence HRV, such as smoking, alcohol consumption, and exercise. These may have affected our overall understanding of how HRV changes under different lifestyle conditions and environmental influences. Therefore, future studies should consider these factors in more detail and explore their relationship with HRV to provide a more comprehensive understanding of the mechanisms of HRV variation in high-altitude immigrants. However, these do not affect the goal of the whole study, which is to seek intervention measures for high-altitude migration. And, in the future, we can also seek personalized interventions from the perspective of individual differences. The mechanism revealed in this study may provide reference for future interventions in high-altitude immigrants from the point of view of erythrocyte function, for example, by increasing the RBCs in high-altitude immigrants within the normal range through dietary therapy or other interventions.

5 Conclusion

In summary, we have identified a neuroimmune pathway rooted in erythrocytes, representing oxygen transport capacity as the basic physiological mechanism that determines human attention performance at high-altitude. Inflammation and HRV mediate the relationship between erythrocytes and attentional function. Our results also confirm the theory of neurovisceral integration model (NIM) at high-altitude. Overall, these findings provide valuable insights into solving the health problems of immigrants who are chronically exposed to high-altitude environments and provide a scientific basis for further research in this area.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Tibet University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

N-NW: Formal analysis, Investigation, Methodology, Resources, Software, Visualization, Writing – original draft, Writing – review & editing. S-FY: Methodology, Writing – original draft. PD: Methodology, Writing – review & editing. RS: Investigation, Writing – review & editing. HL: Investigation, Writing – review & editing. H-LM: Methodology, Writing – review & editing, Conceptualization, Project administration. ML: Conceptualization, Writing – review & editing, Supervision. D-LZ: Conceptualization, Supervision, Writing – review & editing, Project administration.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Immediate and long-term electrophysiological biomarkers of antidepressant-like behavioral effects after subanesthetic ketamine and medial prefrontal cortex deep brain stimulation treatment

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Introduction: Both ketamine (KET) and medial prefrontal cortex (mPFC) deep brain stimulation (DBS) are emerging therapies for treatment-resistant depression, yet our understanding of their electrophysiological mechanisms and biomarkers is incomplete. This study investigates aperiodic and periodic spectral parameters, and the signal complexity measure sample entropy, within mPFC local field potentials (LFP) in a chronic corticosterone (CORT) depression model after ketamine and/or mPFC DBS.

Methods: Male rats were intraperitoneally administered CORT or vehicle for 21 days. Over the last 7 days, animals receiving CORT were treated with mPFC DBS, KET, both, or neither; then tested across an array of behavioral tasks for 9 days.

Results: We found that the depression-like behavioral and weight effects of CORT correlated with a decrease in aperiodic-adjusted theta power (5–10 Hz) and an increase in sample entropy during the administration phase, and an increase in theta peak frequency and a decrease in the aperiodic exponent once the depression-like phenotype had been induced. The remission-like behavioral effects of ketamine alone correlated with a post-treatment increase in the offset and exponent, and decrease in sample entropy, both immediately and up to eight days post-treatment. The remission-like behavioral effects of mPFC DBS alone correlated with an immediate decrease in sample entropy, an immediate and sustained increase in low gamma (20–50 Hz) peak width and aperiodic offset, and sustained improvements in cognitive function. Failure to fully induce remission-like behavior in the combinatorial treatment group correlated with a failure to suppress an increase in sample entropy immediately after treatment.

Conclusion: Our findings therefore support the potential of periodic theta parameters as biomarkers of depression-severity; and periodic low gamma

parameters and cognitive measures as biomarkers of mPFC DBS treatment efficacy. They also support sample entropy and the aperiodic spectral parameters as potential cross-modal biomarkers of depression severity and the therapeutic efficacy of mPFC DBS and/or ketamine. Study of these biomarkers is important as objective measures of disease severity and predictive measures of therapeutic efficacy can be used to personalize care and promote the translatability of research across studies, modalities, and species.

KEYWORDS

electrophysiology, biomarker, depression, behavior, deep brain stimulation, ketamine, psychedelic, translational

1 Introduction

Depression is the most common psychiatric condition globally, affecting an estimated 246 million people in 2020 (Santomauro et al., 2021), with an increasing prevalence in recent years (Goodwin et al., 2022). Importantly, current medications are only effective for 30–40% of patients and require weeks to achieve a therapeutic effect. This leaves an ever-increasing unmet need for more effective treatments (Blackburn, 2019). Mounting preclinical and clinical evidence has increased interest in emerging treatments such as deep brain stimulation (DBS) of the medial prefrontal cortex (mPFC) (Dandekar et al., 2018), as well as subanesthetic doses of ketamine (Bobo et al., 2016). However, how these treatment modalities achieve their therapeutic efficacy is not fully understood.

Oscillatory, or periodic, activity in local field potential (LFP) and electroencephalogram (EEG) recordings has been used to study the neurophysiological effects of both treatment modalities in depression. Nearly every canonical frequency band has been implicated as a potential biomarker or mechanism of depression or remission, especially within the mPFC (Sun et al., 2015; Fitzgerald and Watson, 2018; Jia et al., 2019). However, the majority of previous studies ignored or removed broadband aperiodic changes in the power spectra, potentially confounding the analysis of narrowband periodic activity, as well as missing important physiological information. Therefore, techniques have been developed that algorithmically separate the aperiodic, broadband component from narrowband, periodic peak components. The aperiodic component is parameterized into an exponential function with an exponent describing its steepness and an offset describing its vertical shift, while the periodic peaks over and above this aperiodic component are described by Gaussian curves possessing amplitude, width, and center frequency parameters (Donoghue et al., 2020). Changes in these aperiodic and aperiodic-adjusted periodic parameters (together known as spectral parameters) in the mPFC due to depression and treatment have been explored in task-based (Stolz et al., 2023) and resting-state paradigms (Huang et al., 2021) in humans, as well as *in-silico* through cortical microcircuit models of depression (Mazza et al., 2023) and novel antidepressants (Guet-McCreight et al., 2024). Besides spectral parameters, sample entropy, a measure of signal irregularity and complexity, has been studied as a potential biomarker and clue regarding the neural changes that underlie depression in humans (Faust et al., 2014; Acharya et al., 2015; Čukić et al., 2020; Lin et al., 2020), as it has been shown to represent the functional activity, processing, and connectivity of a region (Wang et al., 2018). However, less work has been done after treatment (Maltbie et al., 2020), or in reverse translating these findings to rodents (Zheng et al., 2012). Therefore, this study will be among the first to explore the translatability and utility of both spectral parameterization and sample entropy in rodent models of depression and treatment.

Furthermore, despite a wealth of publications investigating ketamine and DBS independently, few studies have directly compared the two within the same study (Willner et al., 2019). Such a comparison can help control for differing methodologies in behavioral assays, electrophysiological recording procedures, and analysis techniques. Additionally, no studies have attempted to combine these treatment modalities, despite evidence of overlapping mechanisms, such as beta and gamma power modulation (Bambico et al., 2015; Jett et al., 2015; Sun et al., 2015; Sumner et al., 2020). Furthermore, few preclinical studies have connected long-term changes (>24 h) in mPFC activity after DBS or ketamine treatment with the immediate changes in the region, or the sustained antidepressant-like behavioral effects. In the present study, we investigate electrophysiological changes in the rat mPFC (prelimbic cortex), and behavioral effects of mPFC DBS and/or ketamine administration in a chronic corticosterone (CORT) preclinical model of depression (Sterner and Kalynchuk, 2010). We hypothesized that a combination of ketamine and DBS would induce synergistic behavioral and electrophysiological antidepressant-like effects. LFP recordings immediately, one day, and eight days after treatment administration were compared to baseline recordings and between groups, and then correlated with depression- or remission-like performance in a behavioral assay. We hypothesized that changes in the activity of the mPFC would parallel the depression-like action of CORT and the antidepressant-like action of ketamine and mPFC DBS, and could therefore act as biomarkers.

2 Methods

2.1 Animal numbers, housing, and groups

42 male 6–8 week old (350 ± 50 g) Sprague Dawley rats (Charles River Laboratories, Wilmington, MA) were obtained. The animals acclimated to the facilities for 1 week before experimental procedures began. Animals had access to food and water *ad libitum*, except for 24 h preceding Sucrose Preference Tests (SPT). The animals were single-housed in a controlled environment at 23 ± 1°C, 55–65%

relative humidity, and a fixed 12 h light/dark cycle with lights on at 0600. All procedures performed were approved by the University of Southern California Institutional Animal Care and Use Committee. Animals were weighed and observed daily for the duration of the experiment. The animals were randomly placed into one of five groups: control ($n = 8$), CORT ($n = 8$), CORT+KET ($n = 9$), CORT+DBS ($n = 8$), and CORT+DBS+KET ($n = 9$).

2.2 Electrode implantation surgery

An overview of the experimental design is given in Figure 1A. After acclimation, the animals underwent electrode implantation surgery. Under general anesthesia (2–4% isoflurane in O_2 carrier), a midline incision was made in the scalp. Using a digital stereotaxic frame, twisted bipolar tungsten electrodes (P1 Technologies, Roanoke County, Virginia) were inserted into the mPFC (ML: 0.6 mm relative to bregma, AP: 2.5 mm, DV: 4.0 mm) (Figure 1B) and lateral visual cortex (ML: 5.5 mm, AP: −6.0 mm, DV: 2.5 mm; Figure 1C; Paxinos and Watson, 2007). Six partial thickness holes were drilled into the skull, and six stainless steel autoclave-sterilized anchoring screws (#0–80) were threaded into the skull. The electrodes were then anchored in place using methyl methacrylate.

2.3 Pharmacology and stimulation

2.3.1 Corticosterone depression model

On post-surgery days (PSD) 10–30, 40 mg/kg CORT (C2505, Sigma-Aldrich, Milwaukee, WI) was subcutaneously administered, except in the control group which received 5% DMSO/saline vehicle. Previous studies have demonstrated that this dose and duration induces depressive-like symptoms, such as increases in anhedonia, anxiety, and despair, decreases in evoked grooming behavior, impairments in declarative memory, and weight deficits (Sterner and Kalynchuk, 2010). Animals received the CORT dose after LFP recordings, treatment administrations, and behavioral tasks were completed for the day.

2.3.2 Ketamine treatment

On PSD 24–30, 15 mg/kg ketamine hydrochloride (K2753, Sigma-Aldrich, Milwaukee, WI) were intraperitoneally administered to the CORT+KET and CORT+DBS+KET groups. This dose and duration was chosen based on previous studies (Garcia et al., 2008), which show a rescue of several depressive-like symptoms listed in the previous section. Saline vehicle was administered to the control, CORT, and CORT+DBS groups.

2.3.3 Deep brain stimulation treatment

On PSD 24–30 the mPFC electrode of animals in the CORT+DBS and CORT+DBS+KET groups were connected to an isolated pulse stimulator (STG 4008, Warner Instruments LLC, Hamden, CT) via a twisted wire cable. Continuous electrical stimulation was delivered using the following stimulation parameters: 100 microsecond square wave pulses at 130 Hz and current of 80 μA for 30 min. These parameters were selected based on previous literature (Hamani and Nóbrega, 2010; Hamani et al., 2012), which demonstrated a rescue of several depressive-like symptoms listed in the CORT section. Animals in the CORT+DBS+KET group were administered the ketamine dose immediately before stimulation began.

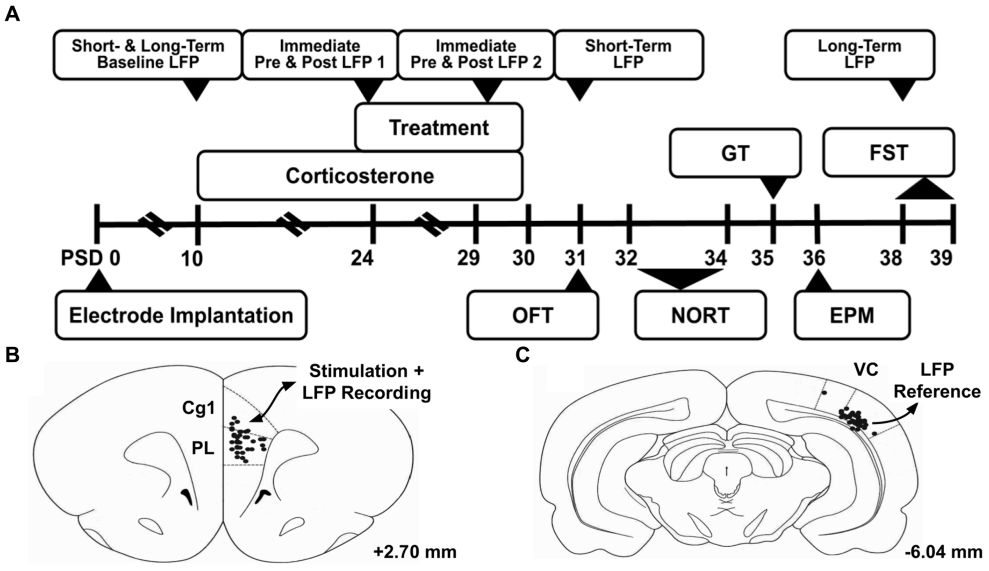

FIGURE 1
Experiment overview. **(A)** Timeline of experiment. **(B)** Electrode tip locations are marked with black dots in the region of interest, the medial prefrontal cortex. This region was the target of the deep brain stimulation treatment, and studied through local field potential (LFP) recordings throughout the experiment. **(C)** Electrode tip locations of the reference electrode in the lateral visual cortex (VC). Atlas illustrations adapted from Paxinos and Watson (2007), and the given coordinates are referenced from bregma. PSD, Post Surgery Day; LFP, Local Field Potential; OFT, Open Field Test; NORT, Novel Object Recognition Test; GT, Groom Test; EPM, Elevated Plus Maze; FST, Forced Swim Test; Cg1, Cingulate Cortex Area 1; PL, Prelimbic Cortex; VC, Visual Cortex.

2.4 Behavioral tests and weight

2.4.1 Open Field Test (OFT)

Non-specific changes in locomotor activity after corticosterone, ketamine, and stimulation (Karatsoreos et al., 2010; Parise et al., 2013; Papp et al., 2022) can confound behavioral and electrophysiological results, therefore we measured average velocity in the Open Field Test on PSD 31. Animals were placed in an open, square arena (50 × 50 cm) and allowed to explore for 10 min. The average speed of locomotion was calculated using the video tracking software TopScan Lite (Clever Sys Inc., Reston, VA). Similarly, non-specific changes in grooming behavior can confound the Groom Test (Planchez et al., 2019), therefore the number of seconds spent spontaneously grooming during the OFT were evaluated.

2.4.2 Novel Object Recognition Test (NORT)

Cognitive dysfunction, including deficits in memory, often occur in depression (American Psychiatric Association, 2013). To measure these, we employed the Novel Object Recognition Test (NORT). In this test, a higher proportion of time spent with a novel object, compared to a familiar object, is interpreted as representing functional object recognition memory (Antunes and Biala, 2012). The methodology employed is in the Supplementary materials. In short, we calculated the average percent change in the Discrimination Index (DI) (difference in time exploring the novel versus familiar object, divided by the total time exploring both objects) between a familiarization day and two test days.

2.4.3 Groom Test (GT)

As healthy rodents groom themselves thoroughly in response to soiling of their coats, reduced evoked grooming in the Groom Test (GT) has been interpreted to represent apathy, a core symptom of depression (Kennedy, 2008; Planchez et al., 2019). The animals performed the GT on PSD 35, their dorsoposterior coats were sprayed with a 10% sucrose solution, and were observed for 10 min in the OFT/NORT arena. Video recordings were evaluated for the number of seconds spent grooming.

2.4.4 Elevated Plus Maze (EPM)

Anxiety is highly comorbid with depression (American Psychiatric Association, 2013), and has been shown to be decreased after ketamine treatment, though whether it relates to its therapeutic efficacy for depression is unclear (Hartland et al., 2023). Therefore, on PSD 36, the Elevated Plus Maze (EPM) was used to measure anxiety, where a higher proportion of time in the innately fear-inducing "open" arms is interpreted as less baseline anxiety (Planchez et al., 2019). The maze and methodology are described in the Supplementary materials.

2.4.5 Forced Swim Test (FST)

Despair, the second core symptom of depression beside apathy (Kennedy, 2008), is typically measured in rodents via the Forced Swim Test (FST), where increased immobile time in the test trial putatively represents despair (Planchez et al., 2019). On PSD 38, the animals were habituated to the FST testing chamber (glass cylindrical tub 50 cm tall, 25 cm diameter, filled with 21°C water 40 cm high) for 10 min. On PSD 39, the animals were tested for 5 min. A video recording of these five minutes was analyzed to determine the number of seconds spent immobile. After each trial the animals were placed in a heated chamber, dried, and monitored for full recovery.

2.4.6 Weight

Weight deficits are another common symptom of depression (American Psychiatric Association, 2013). Furthermore, similar to locomotor activity, non-specific changes in weight can confound behavioral results. Therefore, weights were measured at the "pre" CORT/treatment time point PSD 8–10, as well as the "post" time points PSD 30–32 and 37–39. Relative weights were calculated by dividing an animal's weight at the "post" time points by the "pre" time point. The average of three days was used due to high variability in weight caused by the SPT fasts.

2.5 Local field potential recordings and preprocessing

To provide a baseline from which to track the short- and long-term oscillatory changes induced by chronic CORT and treatment, a 10 min local field potential (LFP) recording of the mPFC was taken on PSD 10, prior to the first CORT dose, using a Cheetah Digital Lynx SX Data Acquisition System (Neuralynx, Bozeman, MT). To investigate long-term changes following the last CORT and/or treatment administration on PSD 30, 10 min LFP recordings on PSD 31 and PSD 38 were taken. To investigate the immediate oscillatory effects induced by treatment administration, 10 min baseline and 20 min post-treatment recordings were taken on PSD 24 and PSD 29, after stimulation was turned off.

These recordings were referenced against an arbitrary cortical region, the lateral secondary visual cortex (V2L). To standardize recording quality, segments at least 3 s long and containing less than 2% noise (values above a threshold determined via visual inspection) were analyzed. Power spectral density plots were generated using the pwelch() function in MATLAB R2019b (MathWorks, Natick, MA). All recordings occurred in a designated arena (30 cm x 46 cm x 19 cm) while the animals were awake, during the light phase of the animals' circadian rhythms.

2.6 Spectral parameter and sample entropy calculations

To parameterize the power spectral density plots generated for each recording, the MATLAB wrapped spectral parameterization (FOOOF) algorithm (version 1.1.0) (Donoghue et al., 2020) was applied to the raw signal segments with the following settings: peak width limits: [0.5, 25], max number of peaks: 5, and aperiodic mode: 'no knee', across the frequency range 1–50 Hz. This produced power spectral density plots for the periodic and aperiodic components of the original plot. Subtracting the aperiodic component from the periodic generated an aperiodic-adjusted power spectral density plot. We found consistent peaks in the theta range (5–10 Hz) and extracted the average center frequency and width of the peaks detected in each range, weighted by the height. Peaks in the low gamma range (20–50 Hz) were detected less consistently and with more variability in peak parameters. We extracted the average center frequency and width of the peaks, weighted by the width. Theta and low gamma

power were calculated by summing the area under the aperiodic-adjusted power spectral density plot curve within each range. We also extracted the aperiodic parameters, the offset (also known as total broadband power) and the exponent (the slope of the extracted aperiodic power spectral density plot), across the 1–50 Hz range.

Additionally, sample entropy, a measure of signal irregularity, was calculated by applying the sampen() MATLAB function to the 1–50 Hz bandpass-filtered signal, divided into samples of length $n = 5{,}000$ (Martínez-Cagiga, 2018). Sample entropy measures the negative natural logarithm of the conditional probability that a sequence that matches for m points will continue to match at the next point, within a tolerance r. Therefore, a high sample entropy value signifies higher irregularity or unpredictability in the data because it reflects a low probability of finding matching sequences. Because the value of sample entropy depends heavily on the choice of m and r parameters, we calculated its value across the ranges of m (2, 3, 4) and r (0.1, 0.15, 0.2, 0.25) recommended when studying biological systems (Molina-Picó et al., 2011). As one aim of this study is to find electrophysiological biomarkers that can differentiate between healthy, depression-like, and remission-like neural activity, we then compared each combination of parameters (Supplementary Figures S1, S4) to select the one with the most between- and within-group differences.

Percent change in spectral parameters and sample entropy was calculated by subtracting the value obtained during baseline recording (pre-CORT: PSD 10; pre-treatment: PSD 24 and 29) from the value in the recording of interest (post-CORT: PSD 31 and 38; post-treatment: PSD 24 and 29), dividing by the value of the baseline recording, and multiplying by 100.

2.7 Statistical analysis

Statistical analyses were performed using R 4.2.2 (R Core Team, 2022). Two-sample t-tests and/or ANOVA were used to compare between groups, while one-sample tests revealed if a group changed significantly relative to their baseline (percent change/mu = 0). Standard parametric tests (one- or two sample t-test, ANOVA, Pearson's r) were used when assumptions of normality and homoscedasticity were met and unless otherwise stated, while non-parametric tests (one- or two-sample Wilcoxon rank sum test, aligned rank transformed (ART) ANOVA, Spearman's ρ/rho) were used otherwise. Multiple test corrections were done with the False Discovery Rate method. For all tests, alpha was set to 0.05 (two-tailed). Experimenters were blinded to the animal's condition during behavioral test evaluation.

2.8 Histology

On PSD 39, rats were euthanized by anesthesia (Isoflurane) and were transcardially perfused with 100 mL of 0.1 M sodium phosphate buffer saline (PBS, pH −7.4), followed by 50 mL of 4% paraformaldehyde (pH 7.4). Brains were extracted and stored in 4% paraformaldehyde at 4°C. Serial coronal sections were cut at 100-μm thickness with a vibratome (Leica VT 1200; Leica Biosystems, Buffalo Grove, IL) starting at +3.8 mm Bregma and ending at −6.50 mm Bregma. Sections in the vicinity of electrodes were mounted onto 0.1% gelatin-subbed slides and stained with NeuroTrace 530/615 Red Fluorescent Nissl Stain (N21482, ThermoFisher Scientific, Waltham, MA, USA) to confirm proper placement (Figures 1B,C).

3 Results

3.1 Chronic CORT and treatment induced differences in depression-related behavioral measures and weight

One-way ANOVAs were done on the results of the behavioral assay to determine whether there were differences between groups. Significant group effects were found in the Groom Test [$F(4,1) = 2.75$, $p = 0.049$, ART ANOVA], Forced Swim Test [$F(4,1) = 3.47$, $p = 0.017$, ART ANOVA], relative weight on PSD 31 [$F(4,1) = 12.85$, $p < 0.001$] and PSD 38 [$F(4,1) = 6.31$, $p < 0.0001$], and locomotion in the OFT [$F(4,1) = 2.99$, $p = 0.031$]. No significant group effects were observed in spontaneous grooming in the OFT, the Elevated Plus Maze, or the Novel Object Recognition Test.

3.1.1 Chronic CORT administration induced apathy-like symptoms in the GT, which was fully rescued by separate repeated DBS or ketamine treatment, but not by the combinatorial treatment

Specific behavioral differences between groups were explored through post-hoc tests, as shown in Figure 2. During the GT (Figure 2A), the CORT group spent significantly less time grooming than the control group (Supplementary Table S1, Row 1), indicating apathy-like symptoms had been induced. The groups that received DBS or ketamine treatment separately spent significantly more time grooming than the CORT group, representing a rescue of apathy-like symptoms. In contrast, the CORT+DBS+KET group did not significantly differ from the CORT group, suggesting apathy-like symptoms were not rescued. In addition, non-specific alterations in grooming activity can confound the GT, however, spontaneous grooming in the OFT did not differ between groups (Figure 2B).

3.1.2 Chronic CORT administration induced despair-like behavior in the FST, which was rescued by chronic DBS, ketamine, and the combinatorial treatment

The CORT group spent more time immobile in the FST (Figure 2C), compared to the control group, indicating despair-like symptoms had been induced (Supplementary Table S1, Row 2). This behavior was rescued in all three treatment groups, as they spent less time immobile than the CORT group.

3.1.3 Anxiety (EPM) and object recognition memory (NORT) measures were unaltered by chronic CORT, however DBS improved NORT performance

In the NORT (Figure 2D), the percent change in DI was greater in the CORT+DBS group than the CORT group (Supplementary Table S1, Row 3). This indicates an improvement in object memory, however, as there was no deficit in the CORT group compared to the control group, this does not represent a "rescue" of memory function. There were no differences in open arm time

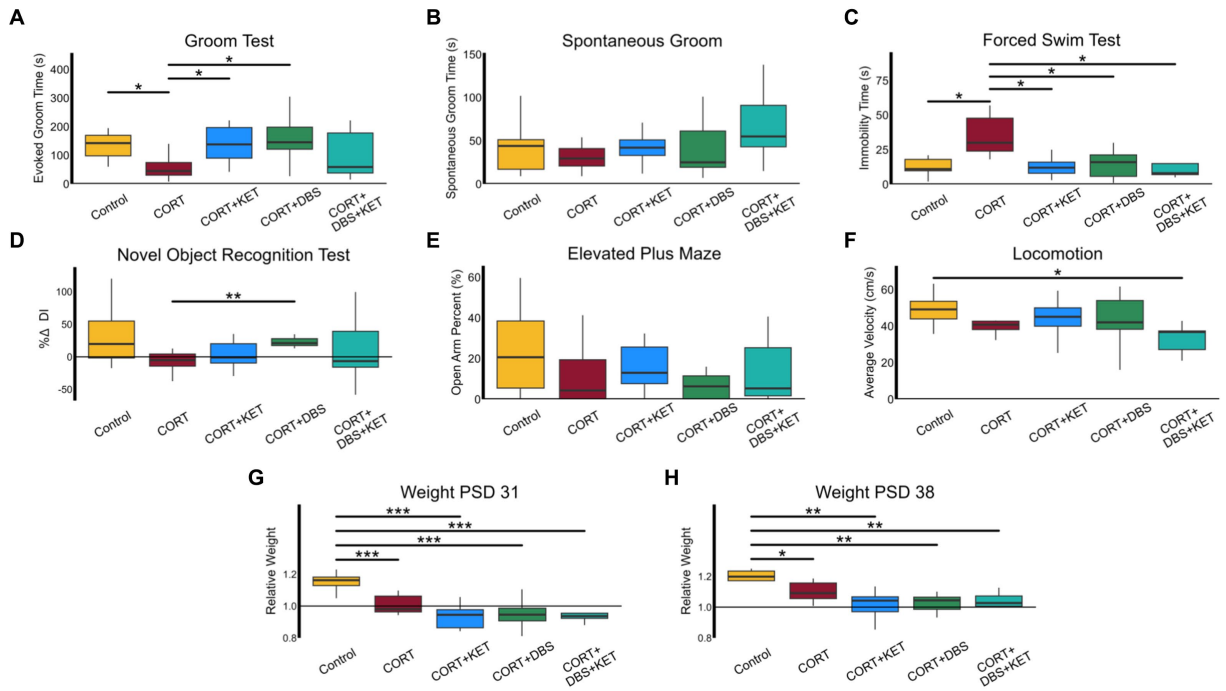

FIGURE 2
Behavioral and weight changes. **(A)** The CORT group ($n = 8$) spent significantly less time grooming than the control group ($n = 8$) indicating apathy-like symptoms were induced in the CORT group. The groups that received DBS ($n = 8$) or ketamine treatment ($n = 9$) separately spent significantly more time grooming than the CORT group, representing a rescue of apathy-like symptoms. The CORT+DBS+KET group ($n = 9$) did not significantly differ from the CORT group, suggesting apathy-like symptoms were not rescued. **(B)** Non-specific alterations in grooming activity can confound the GT, however, spontaneous grooming behavior in the OFT did not differ between groups. **(C)** The CORT group spent more time immobile in the FST compared to the control and treatment groups, indicating despair-like symptoms had been induced in the CORT group, and rescued by all treatment strategies. **(D)** In the NORT, the percent change in Discrimination Index (DI), a measure of object recognition memory, was greater in the CORT+DBS group than the CORT group. **(E)** There were no differences in open arm time percentage in the EPM, a measure of anxiety-like behavior. **(H)** The average velocity of the CORT+DBS+KET group in the OFT was lower than the control group. Relative weight in all groups administered CORT was less than in the control group on **(F)** PSD 31 and **(G)** PSD 38, indicating depression-like weight disturbances were induced, and were not rescued by any treatment strategy. *$p < 0.05$ in FDR-corrected two-sample tests; **$p < 0.01$; ***$p < 0.001$; PSD, Post Surgery Day; CORT, Corticosterone; DBS, Deep Brain Stimulation; KET, Ketamine; GT, Groom Test; FST, Forced Swim Test; NORT, Novel Object Recognition Test; DI, Discrimination Index; EPM, Elevated Plus Maze; OFT, Open Field Test.

percentage in the EPM between the CORT and control or treatment groups, indicating that, as has been previously reported after chronic corticosterone (Bertholomey et al., 2022), comorbid anxiety-like symptoms were not induced (Figure 2E).

3.1.4 Chronic CORT induced weight disruptions that were not rescued by any treatment, and long-term locomotor activity was only altered in the CORT+DBS+KET group

No groups differed from the CORT group in average velocity in the OFT (Figure 2F), though the CORT+DBS+KET group had lower average velocities than the control group (Supplementary Table S1, Row 4). This indicated that while chronic CORT, alone or in combination with repeated ketamine or mPFC DBS, did not induce a deficit in locomotion, a combination of all three reduced average velocity.

The average relative weight in the CORT group was less than in the control on PSD 31 (Figure 2G) and PSD 38 (Figure 2H), indicating depression-like weight deficits had been induced. The three treatment groups did not differ from the CORT group, and had lower relative weights than the control group on PSD 31 (Supplementary Table S1, Row 5) and PSD 38 (Supplementary Table S1, Row 6). Therefore none of the treatment strategies tested rescued these deficits in weight.

3.2 mPFC LFP spectral parameters and sample entropy were modulated immediately after treatment

To investigate the acute effects of treatment administration on mPFC LFP, we calculated the percent changes in spectral parameters and sample entropy immediately before and after treatment on PSD 24 and 29. The pre- (black) and post-treatment (colored) aperiodic-adjusted power spectrum density plots for each group is shown in Figure 3A. For spectral parameters, uncorrected two-way ANOVAs with group and day effects found significant group effects for the following spectral parameters: offset [$F(4,1) = 4.60$, $p < 0.01$, ART ANOVA], and exponent [$F(4,1) = 4.21$, $p = 0.011$, ART ANOVA]. Theta peak frequency [$F(4,1) = 2.55$, $p = 0.056$] and power [$F(4,1) = 2.09$, $p = 0.095$] showed trends strong enough to warrant further post-hoc analysis. No day effects were found, and there were no significant group x day interactions for any parameter, therefore, the average of both

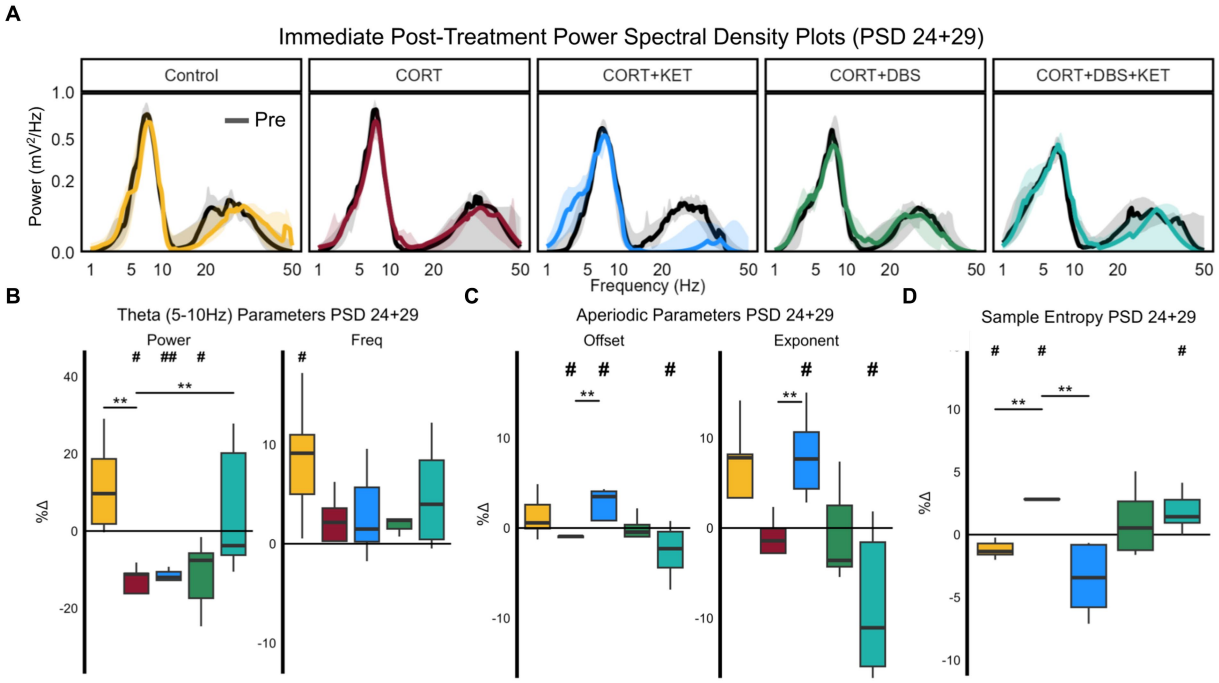

FIGURE 3
Changes in spectral parameters and sample entropy immediately post-treatment, PSD 24+29. **(A)** Median aperiodic-adjusted periodic power spectrum density plots of the local field potential recordings on PSD 24+29 immediately pre- (black) and post-treatment (colored) for each group. **(B)** Boxplots of the percent change in periodic theta (5–10 Hz) spectral parameters aperiodic-adjusted power (mV^2/Hz) and peak frequency (Hz). Theta power significantly decreased relative to the pre-treatment baseline in the CORT, CORT+KET, and CORT+DBS groups (indicated by '#'). In the CORT group, this significantly differed from the control and CORT+DBS+KET groups (indicated by '*'). Theta peak frequency increased significantly in the control group. **(C)** Boxplots of the percent change in the aperiodic spectral parameters offset and exponent. The offset was significantly increased in the CORT+KET group relative to baseline and the CORT group, which decreased significantly from baseline. Similarly, the offset significantly decreased in the CORT+DBS+KET group relative to baseline. The exponent also increased significantly compared to baseline and the CORT group, and the CORT+DBS+KET group decreased relative to baseline. **(D)** Boxplots of the percent changes in sample entropy. Sample entropy significantly increased in the CORT group relative to the control and CORT+KET groups, and the control group decreased significantly relative to baseline. Sample entropy in the CORT+DBS+KET group also increased significantly relative to pretreatment baseline (*, #$p < 0.05$ in one/two sample tests; **, ##$p < 0.01$); CORT, Corticosterone; PSD, Post Surgery Day; DBS, Deep Brain Stimulation; KET, Ketamine; Freq, Peak Frequency.

days was used for the post-hoc analyses. For sample entropy, two-way, multiple-test corrected ANOVAs found significant group effects for all parameter combinations. We selected the parameter combination $r = 0.25$ and $m = 4$ (Supplementary Figure S1) for further analysis [$F(4,1) = 6.03$, $p < 0.01$], as post-hoc tests revealed the strongest between- and within-group differences.

3.2.1 Periodic parameters were modulated by CORT and all treatments

Theta power decreased relative to pre-treatment baseline on PSD 24+29 significantly in the CORT, CORT+KET, and CORT+DBS groups (Figure 3B; Supplementary Table S2, Row 1). For the CORT group, this differed significantly from the control and CORT+DBS+KET groups, which did not change. Meanwhile, theta peak frequency significantly increased relative to baseline in the control group, which differed trendwise from the CORT group which did not change.

In the control group, low gamma peak frequency increased significantly relative to baseline and trendwise relative to the CORT group (Supplementary Figure S2A). Meanwhile, low gamma peak width increased trendwise relative to the CORT group in the CORT+KET and CORT+DBS groups.

3.2.2 Aperiodic parameters were modulated in both ketamine treated groups

The offset significantly increased in the CORT+KET group immediately after treatment on PSD 24+29 relative to both baseline and the CORT group, which decreased significantly relative to the pretreatment baseline (Figure 3C; Supplementary Table S2, Row 2). In contrast, the offset decreased trendwise in the CORT+DBS+KET group relative to baseline.

Changes in the exponent were very similar. The exponent increased in the control (trendwise) and CORT+KET group (significant) relative to the pretreatment baseline and the CORT group. In contrast, the exponent of the CORT+DBS+KET group decreased significantly compared to baseline and trendwise compared the CORT group.

3.2.3 Sample entropy decreased in the control and CORT+KET group, while it increased in the CORT and CORT+DBS+KET group

Sample entropy significantly decreased in the control and CORT+KET groups relative to their baseline and the CORT group immediately after treatment on PSD 24+29 (Figure 3D; Supplementary Table S2, Row 3). Meanwhile, the CORT and CORT+DBS+KET group both significantly increased in sample

entropy relative to their pretreatment baseline. The CORT and CORT+DBS+KET groups increased relative to baseline across all parameter combinations tested (Supplementary Figure S1), while the control group increased in 7 of 12 pairings. Furthermore, the control and CORT groups significantly differed in every pairing, while the CORT and CORT+KET groups differed in all but one.

3.3 mPFC spectral parameters and sample entropy were altered in the short- and long-term post-CORT and treatment

To explore the short- and long-term effects of CORT and treatment on mPFC LFP spectral parameters and sample entropy, we calculated the percent changes in these measures between a pre-CORT baseline on PSD 10, and two time points after the last CORT and treatment administration on PSD 30. By the short-term time point, PSD 31, one-way ANOVAs found group differences in theta peak frequency [$F(4,1) = 2.90$, $p = 0.045$] and the exponent [$F(4,1) = 5.14$, $p < 0.01$]. The PSD 10 (black) and PSD 31 (colored) aperiodic-adjusted power spectrum density plots for each group are shown in Supplementary Figure S3A. Post-hoc tests found that while theta peak frequency decreased in both the CORT and CORT+KET, the CORT+KET group decreased significantly more relative to the CORT group (Supplementary Figure S3B; Supplementary Table S2, Row 4). For the exponent, the control group increased trendwise relative to the CORT group (Supplementary Figure S3C; Supplementary Table S2, Row 5). Within-group tests found that relative to the pre-CORT baseline, the offset and exponent significantly decreased in the CORT+DBS group. A one-way ANOVA found no effect by group in sample entropy for any parameter combination by PSD 31.

By the long-term time point, PSD 38, uncorrected one-way ANOVAs found significant group effects in theta power [$F(4,1) = 3.39$, $p = 0.026$] and peak frequency [$F(4,1) = 3.39$, $p = 0.026$], as well as exponents [$F(4,1) = 5.85$, $p < 0.01$]. The PSD 10 (black) and PSD 38 (colored) aperiodic-adjusted power spectrum density plots for each group are shown in Figure 4A. For sample entropy, one-way ANOVAs found a trend in group effects for one parameter combination, $r = 0.25$ and $m = 4$ [Supplementary Figure S4; $F(4,1) = 2.46$, $p = 0.075$].

3.3.1 Theta power, peak frequency, and peak width were modulated in the long-term by CORT, ketamine, and DBS

Theta power by PSD 38 decreased significantly in the CORT, CORT+KET, and CORT+DBS+KET groups relative to baseline (Figure 4B; Supplementary Table S2, Row 6). Theta power decreased trendwise more in the CORT+KET group compared to the CORT group. Furthermore, in control, CORT, and the CORT+KET group, theta peak frequency decreased significantly relative to baseline. Like power, theta peak frequency decreased trendwise more in the CORT+KET group compared to the CORT group.

3.3.2 Low gamma parameters decreased in the CORT and CORT+KET groups

Low gamma power (trendwise), peak frequency (significant), and peak width (significant) decreased relative to baseline by PSD 38 in the CORT group (Supplementary Figure S2C; Supplementary Table S3, Row 6). Similarly, low gamma peak frequency decreased trendwise by PSD 38 in the CORT+KET group.

3.3.3 The aperiodic parameters were modulated in the long-term by CORT and ketamine

The exponent significantly decreased by PSD 38 in the CORT and CORT+DBS groups (Figure 4C; Supplementary Table S2, Row 7) relative to pre-CORT baseline, while it increased trendwise in the CORT+KET group. For the CORT group, this differed significantly from the CORT+KET group, and trendwise from the control and CORT+DBS+KET groups. Furthermore, the offset decreased trendwise in the CORT group, which differed significantly from the CORT+KET group and trendwise from the CORT+DBS+KET group.

3.3.4 Sample entropy was normalized by DBS or ketamine separately, but not combined

By PSD 38, sample entropy was significantly lower in the control, CORT+KET, and CORT+DBS groups compared to the CORT group (Figure 4D; Supplementary Table S2, Row 8), which had increased relative to its baseline. The CORT+KET group decreased trendwise from its baseline. It should be noted that while the control and CORT+KET groups differed from the CORT group in all 12 parameter combinations, the CORT and CORT+DBS groups only differed in one parameter combination (Supplementary Figure S4). The CORT group increased significantly from baseline in seven parameter combinations.

3.4 Electrophysiological measures and cognitive behavioral measures correlated with the Groom and Forced Swim Tests

We then explored the linear relationships between electrophysiological and behavioral measures throughout the experiment. The p-values of Pearson or Spearman's linear correlation coefficients were calculated for several types relationships. To best investigate which measures related to the depression- and remission-like differences between the CORT group and the control or treatment groups, we pooled the results of each group with those of the CORT group to create a "group pool." Only measures that significantly differed from baseline or from the CORT group were tested for correlation.

3.4.1 Immediate, short- and long-term post-treatment electrophysiological and cognitive changes correlated with depression- and remission-like behavior

We first explored the relationship between the depression-related measures, the Groom Test (GT) on PSD 35 and the Forced Swim Test (FST) on PSD 39, and the long-term electrophysiological changes on PSD 38. Electrophysiological correlates of behavior at this time parallel clinical biomarkers for steady-state depression or remission, given the extended time since the last CORT or treatment administration (eight days). Furthermore, as this is the time point closest to the GT and FST, these electrophysiological correlates may provide evidence of the mechanism underlying the long-term depression-related behavioral effects of CORT and the treatment strategies. For the control group pool, healthy performance in the Groom Test correlated with the increase in theta peak frequency in

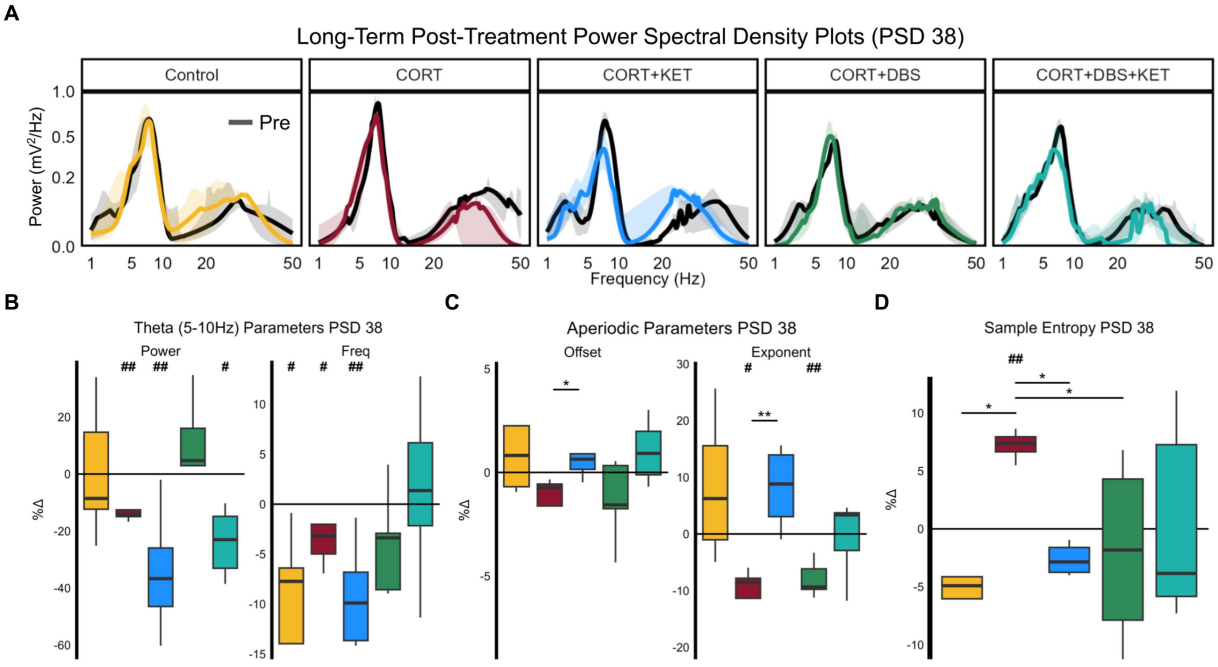

FIGURE 4
Changes in spectral parameters and sample entropy eight days post-treatment, PSD 38. **(A)** Median aperiodic-adjusted periodic power spectrum density plots of the baseline (black) local field potential recordings on PSD 10, and the long-term post-treatment recording on PSD 38 (colored). **(B)** Boxplots of the percent change in periodic theta (5–10 Hz) spectral parameters aperiodic-adjusted power (mV^2/Hz) and peak frequency (Hz). Theta power decreased in the CORT, CORT+KET, and CORT+DBS+KET groups relative to baseline (indicated by '#'). In the control, CORT, and CORT+KET group, theta peak frequency decreased. **(C)** The offset and exponent increased significantly in the CORT+KET group relative to the CORT group. The exponent decreased relative to baseline in the CORT and CORT+DBS groups. **(D)** Boxplots of the percent change in sample entropy, which was significantly higher in the CORT group compared to the control, CORT+KET, and CORT+DBS groups, as well as the pre-CORT baseline (*, #$p < 0.05$ in uncorrected one/two sample tests; **, ##$p < 0.01$); CORT, Corticosterone; PSD, Post Surgery Day; DBS, Deep Brain Stimulation; KET, Ketamine.

the control group (Figure 5A; Supplementary Table S3, Row 1). In the CORT+DBS group pool, remission-like performance in the Groom Test correlated with the increase in low gamma peak width in the treated group compared to the CORT group (Figure 5B). In the CORT+KET group pool, the Groom Test correlated with the increase in the exponent (Figure 5C) and offset, as well as the decrease in sample entropy (Figure 5D), in the CORT+KET group relative to the CORT group and its baseline. In addition, remission-like performance in the Forced Swim Test correlated with the increase in offset compared to the CORT group (Figure 5E).

Similarly, the second set of correlations examined the relationships between the depression-related measures (FST, GT), and short-term (PSD 31) electrophysiological and cognitive changes. In the control group pool, correlates at this time point parallel clinical biomarkers that track the early stages of depression after exposure to prolonged stress. In this pool, the increased exponent in the control group compared to the CORT group correlated with the GT (Figure 5F; Supplementary Table S3, Row 2). In contrast, in the treatment group pools, correlates at this time point parallel clinical biomarkers measured one day after treatment offset that may predict long-term remission. For the CORT+KET group pool, the increase in the exponent in the treated group also correlated with the GT (Figure 5F), while in the CORT+DBS group pool the improvement in the object memory task, the NORT, in the treated group correlated with the GT (Figure 5G). In addition, the decreased offset of the CORT+DBS group correlated with the FST (Figure 5H).

We then related the immediate electrophysiological changes post-treatment (PSD 24+29) with the depression-related GT and FST behavioral tasks. Here, the control group pool correlates are intended to represent biomarkers of the chronically-stressed mPFC dysfunctionally responding to acute stress, in this case the mild stress of restraint, intraperitoneal saline injection, and sham stimulation. In this group pool, we see that the increase of theta power in the control, compared to the decrease of the CORT group, correlated with their GT performance (Figure 6A; Supplementary Table S3; Row 3). Meanwhile, in the treatment group pools, these correlates represent biomarkers measured immediately after treatment administration that may predict long-term remission. In the CORT+DBS group pool, the increase in low gamma peak width (Figure 6B) and offset (Figure 6C) in the treated group, compared to the CORT group, correlated with the GT. Similarly, in the CORT+KET group pool, the increase in the offset relative to the CORT group and the baseline in the treated group also correlated with the GT (Figure 6D). In addition, the FST correlated with both the exponent (Figure 6E) and the offset (Figure 6F). Finally, in all four group pools, sample entropy immediately after treatment correlated with the GT (Figure 6G).

3.4.2 Putative electrophysiological and cognitive biomarkers correlated with one another across time

We then investigated whether the electrophysiological and behavioral biomarkers of depression-related behavior were correlated

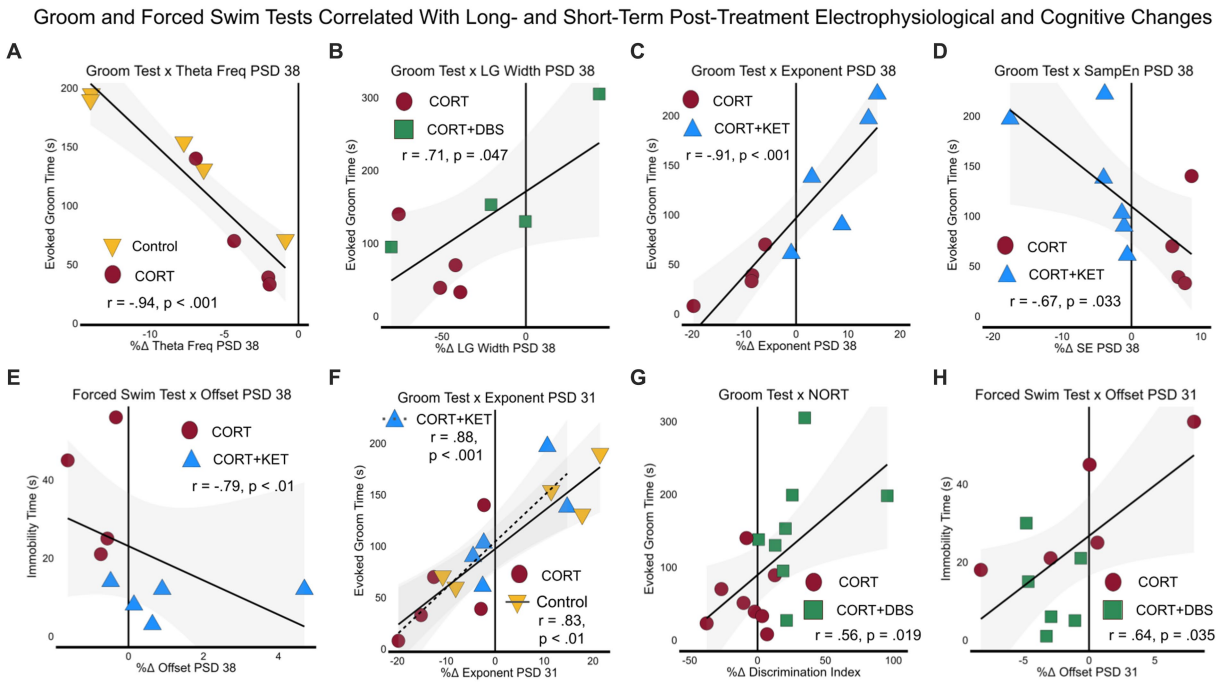

FIGURE 5
Linear regressions and correlation coefficients for the relationships between depression-related behavior and sustained post-treatment electrophysiological or cognitive changes. Depression-related behavioral measures GT (PSD 35) and FST (PSD 39) were correlated with short- (one day after last treatment, PSD 31) and long-term (eight days after last treatment, PSD 38) electrophysiological or cognitive (NORT, PSD 32–34) changes. Each group was pooled with the CORT group to create a "group pool." **(A)** Theta peak frequency on PSD 38 negatively correlated with the GT in the control group pool. **(B)** In the CORT+DBS group pool, low gamma peak width on PSD 38 positively correlated with the GT. For the CORT+KET group pool on PSD 38, **(C)** the aperiodic exponent positively and **(D)** sample entropy negatively correlated with the GT, while **(E)** the aperiodic offset negatively positively correlated with the FST. **(F)** In both the control and CORT+KET group pools, the exponent on PSD 31 positively correlated with the GT. **(G)** In the CORT+DBS group pool, the NORT positively correlated with the GT, while **(H)** the offset on PSD 31 positively correlated with the FST. PSD, Post Surgery Day; CORT, Corticosterone; DBS, Deep Brain Stimulation; KET, Ketamine; GT, Groom Test; FST, Forced Swim Test; NORT, Novel Object Recognition Test; DI, Discrimination Index; Theta Freq, Theta Peak Frequency; SampEn/SE, Sample Entropy; LG, Low Gamma.

across the experiment, as this could hint at potential neural mechanisms of action for CORT and the treatment strategies. For each group pool, we first correlated the electrophysiological biomarkers from the long-term time point PSD 38, which have the potential to be causally related to performance on the GT and FST, with electrophysiological changes at the short-term post-treatment time point PSD 31. Those correlated PSD 31 measures were then correlated with the measures taken immediately after treatment on PSD 24+29. In the control group pool, the increase in theta peak frequency in the control group on PSD 38 correlated with the increase in the exponent in the control group on PSD 31 (Supplementary Figure S5A; Supplementary Table S3, Row 4). In turn, the increase in the exponent of PSD 31 correlated with the increase in theta power immediately after sham treatment on PSD 24+29 (Supplementary Figure S5B; Supplementary Table S3, Row 5). In the CORT+KET group pool, the decreased sample entropy in the treated group compared to the CORT group on PSD 38 correlated with the decrease in theta peak frequency on PSD 31 (Supplementary Figure S5C). In turn, the decrease in theta peak frequency on PSD 31 correlated with the decrease in sample entropy (Supplementary Figure S5D) and increase in offset and low gamma peak width immediately after treatment on PSD 24+29. For the same group pool, the decreased exponent (Supplementary Figure S5E) and offset, as well as the increased sample entropy (Supplementary Figure S5F) on PSD 38 in the CORT+KET group correlated with the increased exponent on PSD 31. In turn, the increased exponent on PSD 31 correlated with the decreased sample entropy immediately after treatment on PSD 24+29 (Supplementary Figure S5G). Finally, in the CORT+DBS group pool, improved performance in the NORT in the treated group correlated with the immediate increase in low gamma peak width immediately after treatment (Supplementary Figure S5).

3.4.3 Depression-related weight deficits correlated with sample entropy and the exponent

To investigate the relationship between mPFC electrophysiological measures and the weight deficits observed in the CORT group, we performed similar analyses as in the first two sections for the control group pool. Decreased relative weight at the long-term time point on PSD 38 correlated with a decreased exponent on PSD 38 in the CORT group (Supplementary Figure S6A; Supplementary Table S3, Row 6). This decrease on PSD 38 correlated with a decrease in the exponent at the short-term time point (Supplementary Figure S6B). In turn, as described in section 4.4.2, the increase in the exponent on PSD 31 correlated with the increase in theta power immediately after sham treatment. Meanwhile, weight deficits on PSD 31 correlated with the decrease in the exponent (Supplementary Figure S6C) and increase in sample entropy (Supplementary Figure S6D) immediately after treatment.

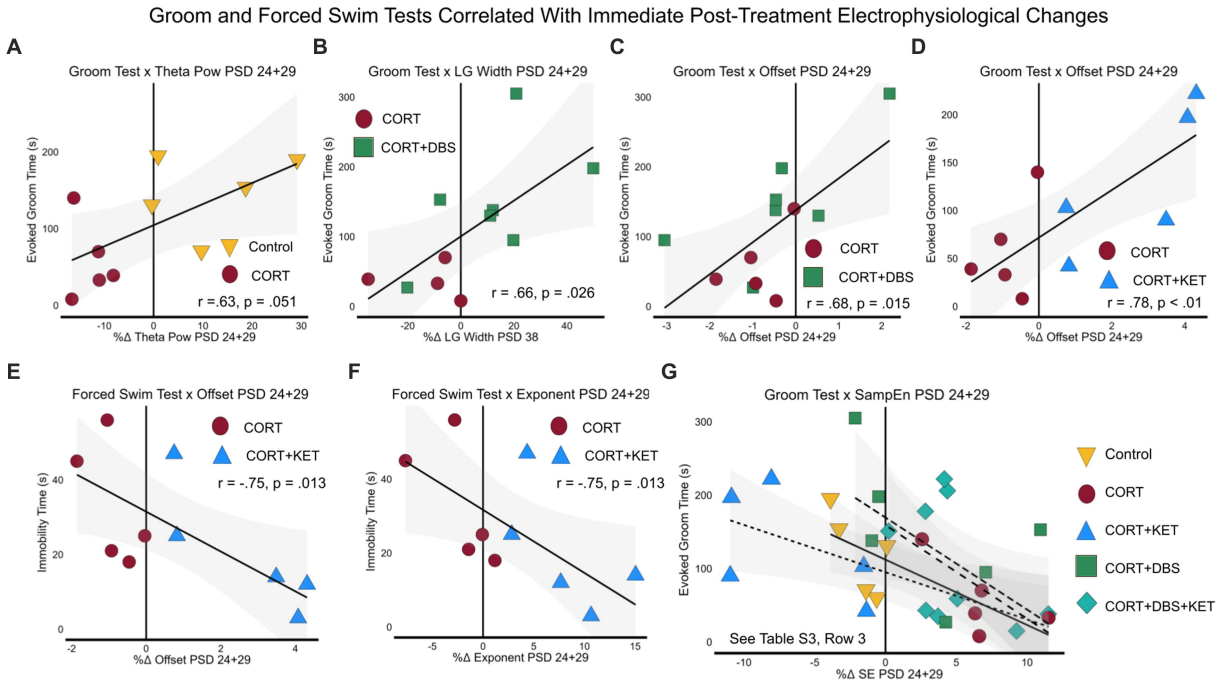

FIGURE 6
Linear regressions and correlation coefficients for the relationships between long-term depression-related behavior and immediate post-treatment electrophysiological measures. Depression-related behavioral measures GT (PSD 35) and FST (PSD 39) were correlated with significant immediate post-treatment (PSD 24+29) electrophysiological changes. Each group was pooled with the CORT group to create a "group pool." **(A)** Aperiodic-adjusted theta power positively correlated with the GT in the control group pool. In the CORT+DBS group pool, **(B)** low gamma peak width and **(C)** the aperiodic offset correlated with the GT. In the CORT+KET group pool, **(D)** the offset also correlated with the GT, while the FST correlated negatively with both **(E)** the offset and **(F)** the aperiodic exponent. **(G)** Sample entropy negatively correlated with the GT in all four group pools. PSD, Post Surgery Day; CORT, Corticosterone; DBS, Deep Brain Stimulation; KET, Ketamine; GT, Groom Test; FST, Forced Swim Test; NORT, Novel Object Recognition Test; DI, Discrimination Index; Theta Pow, Theta Power; SampEn/SE, Sample Entropy; LG, Low Gamma.

3.4.4 Non-specific motor or metabolic deficits did not confound the depression-related behavioral tasks

To ensure that differences in weight and locomotion did not confound our measures of depression-like behavior, we correlated each pool's relative weights on PSD 38, and their average velocity in the OFT, with evoked groom and immobility time. While locomotion correlated with the GT in the control group pool (Supplementary Table S3, Row 7), there was no significant difference in locomotion between these two groups (Figure 2H). Therefore, this factor could not have driven the differences between groups in the GT. For the CORT+DBS+KET group pool, we also correlated locomotion with electrophysiological measures, however there were no correlations that explained the decreased locomotion in the treatment group. There were no significant correlations between weight and behavior. Overall, these findings are evidence that the deficits observed in the GT and FST were not due to non-specific motor or metabolic deficits.

3.4.5 Sample entropy correlated with the offset, exponent, theta power, and low gamma peak width

As the neural underpinnings of sample entropy are not well understood, we tested whether sample entropy significantly correlated with spectral parameters. In general, sample entropy correlated consistently with the exponent and offset, and at times with theta power and low gamma peak width (Supplementary Figure S6, Row 2; Supplementary Table S3, Row 8/9).

4 Discussion

4.1 Separately, but not combined, DBS and ketamine rescued depression-like behavioral performance induced by CORT, which correlated with changes in mPFC LFP and cognitive measures across time

The aim of this experiment was to investigate the electrophysiological correlates of depression- and remission-like effects of corticosterone, ketamine, and mPFC DBS in rats. Given the key role of the mPFC dysfunction in driving depression symptoms (Pizzagalli and Roberts, 2022), these correlates are not only potential biomarkers for depression severity and treatment efficacy but they also may point at the mechanisms underlying depression- and remission-like behavior. Our stress-based depression model, chronic corticosterone administration, induced apathy-like behavioral performance in the Groom Test, despair-like behavior in the Forced Swim Test, and depression-like weight deficits. While remission-like performance on the FST was induced by ketamine and/or DBS, only ketamine or DBS separately rescued performance on the GT. To find biomarkers of these depression-related measures, we correlated them

with changes in mPFC LFP at three time points post-treatment: immediate (after first and sixth treatment, PSD 24 & 29), short-term (one day after last treatment, PSD 31) and long-term (eight days after last treatment, PSD 38).

4.1.1 Depression-like behavioral and weight effects of chronic CORT correlated with changes in the exponent, sample entropy, and theta parameters

Eight days after chronic CORT administration, we found that a long-term increase in theta peak frequency in the CORT group, compared to the control group, correlated with apathy-like behavior in the GT. At the same time point, a decrease in the exponent correlated with concurrent weight deficits, while earlier, at the short-term, one day post-CORT time point, a decreased exponent in the CORT group correlated with the GT. Together, these periodic and aperiodic markers represent potential biomarkers for early and steady-state depression symptoms after chronic stress. Further, when considering the neural underpinnings of these electrophysiological measures, our findings may point toward the potential long-term mechanisms of corticosterone in inducing depression-like behavioral and weight symptoms. The current understanding of steady-state depression etiology is the hyperactivity and excitability of the mPFC, which drives excessive long-range inhibitory signals to regions involved in motivation, cognition, reward, and emotion (Pizzagalli and Roberts, 2022). Therefore, since a decreased exponent represents decreased inhibition (Lombardi et al., 2017), and chronic stress decreases inhibitory GABAergic transmission in male rodents (Ghosal et al., 2020), these findings support the theory that corticosterone recapitulates the stress-based depression-inducing hyperexcitation of the mPFC (Sterner and Kalynchuk, 2010; Wilber et al., 2011; Arnsten et al., 2023). They also agree with *in-silico* findings regarding decreased exponent values in a inhibitory interneuron knock-down depression model (Guet-McCreight et al., 2024). While the potential role of aberrantly increased theta peak frequency in the depressive symptoms is unclear, we speculate that since hyperactivation of the hippocampal to mpFC pathway, which operates at the theta frequency (Padilla-Coreano et al., 2019), has been correlated with depression severity in humans (De Kwaasteniet et al., 2013; Sambataro et al., 2014) and rodent models (Airan et al., 2007), and the hippocampus operates at a higher theta frequency than the mPFC (Biskamp et al., 2017), perhaps the increase in peak frequency represents the pathway's depression-related hyperconnectivity. However, more work will need to be done to understand the meaning of this potential biomarker.

While the short- and long-term time points represent steady-state depression-like conditions, electrophysiological markers at the immediate time point on PSD 24+29 may represent the depression-inducing, aberrant response of the mPFC to stress (restraint and sham treatment). At this time point, an immediate decrease in theta power and increase in sample entropy in the CORT group correlated with apathy-like performance in the GT, and each other. Sample entropy is a measure of signal irregularity and complexity, and has been shown to correlate with a region's degree of functional activity, processing, and connectivity (Wang et al., 2018). It has also been demonstrated to increase in frontal EEG electrodes in depression patients (Čukić et al., 2020; Lin et al., 2020). Meanwhile, aperiodic-adjusted theta power has been shown to decrease in the mPFC when rats are in a perceived "safe" environment (Adhikari et al., 2010). Therefore, similar to the steady-state decrease in mPFC inhibition discussed previously, we hypothesize that the increase in functional activity and decrease in safety-related theta power during mild stress was indicative of corticosterone's depression-inducing hyperactivation of the mPFC (Sterner and Kalynchuk, 2010; Wilber et al., 2011; Arnsten et al., 2023). Furthermore, we found that the exponent and theta peak frequency on PSD 38 correlated with the exponent on PSD 31, which in turn correlated with the exponent immediately after treatment on PSD 24+29. This consistent and interrelated thread of electrophysiological indicators within the mPFC hints at potential relationships between them, however, causality can not be inferred from the present study.

4.1.2 The remission-like behavioral effects of ketamine correlated with changes in the exponent, offset, and sample entropy

After ketamine treatment alone, we found that a long-term decrease in sample entropy, and an increase in the exponent and offset, significantly correlated with remission of apathy-like behavior in the GT, and despair-like behavior in the FST. At the short-term post-treatment time point PSD 31, one day after the last ketamine treatment, the GT again correlated with an increase in the exponent relative to the CORT group. This was on par with the increase in the control group, which also correlated with the GT. Alone, these findings indicate these three measures may function as biomarkers for long-term treatment efficacy after ketamine. However, when coupled with our growing understanding of the neural dynamics they represent, these measures may also point toward potential mechanisms of ketamine's therapeutic action. As previously discussed, the aperiodic exponent and offset have been correlated with inhibition, and sample entropy has been correlated with functional activity and connectivity. Meanwhile, excessive functional activity and connectivity of the mPFC is central to theories regarding the etiology of depression and CORT-based depression models. Therefore, we hypothesize that the increase in inhibition and decrease in function, in line with the control group, potentially represent ketamine exerting its long-term therapeutic effects by "normalizing" mPFC hyperactivity. Indeed, ketamine increases the inhibitory tone of the mPFC of rats 24h post-treatment (Yin et al., 2021; Mingardi et al., 2023), and reduces the functional connectivity of the human prefrontal cortex for up to two weeks post-treatment (Chen et al., 2019; Siegel et al., 2021). Therefore, the modulation of aperiodic parameters and sample entropy after ketamine are perhaps indicative of this sustained cellular and functional normalization. Interestingly, our finding of an increased exponent in the mPFC after ketamine parallels findings after human electroconvulsive and magnetic seizure therapy (Smith et al., 2023). Furthermore, immediately after treatment, the GT also correlated with acutely decreased sample entropy and increased offset, while the FST correlated with increased offset and exponent. These findings indicate that, in addition to their potential as short- and long-term treatment efficacy biomarkers, these measures also have potential as immediate biomarkers. Similar to our interpretation of the sustained post-treatment electrophysiological correlates, we speculate that these immediate correlates represent processes critical to a rapid mPFC "normalization" mechanism. Rodent studies have found ketamine normalizes mPFC dopaminergic (Wu et al., 2021) and GABAergic signaling (Ghosal et al., 2020), the latter in particular potentially driving the observed normalization of the aperiodic parameters. Meanwhile human MRI signal in the medial frontal cortex is normalized via reductions in

functional activity and connectivity immediately after ketamine during an emotionally-valenced stimulus task (Reed et al., 2018; Morris et al., 2020), potentially paralleling our finding of decreased sample entropy.

Interestingly, in addition to being highly correlated with remission-like behavior and one other at the same time points, sample entropy, offset, and the exponent were also correlated with one another across time points. Tracking these correlations across time may help bridge the gaps in understanding between the relatively well studied immediate correlates of ketamine's efficacy, and the less well understood long-term correlates. Specifically, we found that the three measures correlated with an increase in the exponent at the short-term timepoint, which in turn correlated with decreased sample entropy immediately after treatment. In addition, we found that the long-term decrease in sample entropy correlated with a short-term decrease in the theta peak frequency, which in turn correlated with the immediate decrease in sample entropy, as well as the increase in the offset and low gamma peak width. Interestingly, unlike the other correlates, the shift in theta peak frequency was in the opposite direction of the control group, decreasing even more than in the CORT group. As previously discussed, modulation of peak theta frequency may relate to modulation of the hippocampal-mPFC pathway, which has previously been demonstrated after ketamine in humans (Siegel et al., 2021) and rats (Gass et al., 2019). Meanwhile, resting-state low gamma activity has been shown to increase in the mPFC after ketamine in both rodents (Qin et al., 2023) and humans (Cornwell et al., 2012), which correlated with treatment efficacy in humans (Nugent et al., 2019). Taken together, our findings potentially indicate that the increase of low gamma activity and inhibition, and decrease in complexity, immediately after ketamine treatment drove a short-term increase in inhibition and decrease in theta activity, which culminated in the remission-related long-term increase in inhibition and decrease in complexity. However, as this interpretation is based on correlations, we can not draw definitive conclusions regarding causality.

4.1.3 The remission-like behavioral effects of mPFC DBS correlated with changes in the offset, low gamma parameters, sample entropy, and cognition-related behavior

After mPFC DBS alone, a long-term increase in the low gamma peak width and improvement in cognitive behavior in the NORT correlated with remission-like behavior in the GT. Furthermore, an increased offset at the short-term time point correlated with the FST. Finally, an immediate decrease in sample entropy, as well as the increase in the offset and low gamma peak width, all correlated with the GT. These correlations indicate these measures may serve as biomarkers for the long-term treatment efficacy after DBS, and when considering their neural origins and interrelationships, they may also hint at its mechanism of action. mPFC low gamma activity has previously been shown to increase to healthy levels after mPFC DBS in rodents (Jia et al., 2019) and humans (Scherer et al., 2023), and has been implicated in the cognitive functions of the mPFC, including memory in rodents (Zhang et al., 2019) and humans (Senkowski and Gallinat, 2015). Indeed, in the present study, improvements in object recognition memory in the NORT correlated with the immediate post-treatment increase in low gamma peak width. Furthermore, low gamma power has been shown to be generated via the interplay between glutamatergic and GABAergic neurons (Tort et al., 2013), and interestingly, cognitive deficits stemming from dysfunction of these cell types in the mPFC have been implicated in the etiology of apathy (Levy and Dubois, 2006). Particularly implicated are two components of recognition memory, working memory and episodic memory, which involve the mPFC (Ragozzino et al., 2002; Blumenfeld and Ranganath, 2007), and are measured by the NORT (Antunes and Biala, 2012). Furthermore, working memory performance has been previously correlated with apathy in human schizophrenia patients (Raffard et al., 2016). Therefore, our findings hint that immediate and long-term modulation of glutamatergic and GABAergic neuron interplay may have driven long-term improvements in cognition that then related to remission-like performance in the GT. The translatability of this finding is supported by work in humans showing that mPFC DBS increases gamma activity (Scherer et al., 2023) and improves long-term measures of memory (Runia et al., 2023). Again, we must be cautious in overinterpreting these correlations, more work will need to be done to demonstrate causal links, if any. Furthermore, it is unclear how the immediate and short-term modulation of complexity and inhibition could causally relate to the long-term depression-related behavioral measures given the lack of intermediate correlates and relatively weak modulation, in comparison to ketamine treatment.

4.1.4 The apathy-like behavior of the combinatorial group only correlated with a failure to suppress an increase in sample entropy immediately after treatment

Finally, we hypothesized that a novel combinatorial treatment of ketamine and mPFC DBS would be synergistically effective in its antidepressant-like effect. As in both treatments separately, this strategy rescued despair-like symptoms in the FST, however, it failed to rescue apathy-like symptoms in the GT (Figure 2). To search for an explanation for these counterintuitive findings, we looked for immediate, short- and long-term mPFC LFP correlates of the GT. The only hint we uncovered was a negative correlation with the increase in sample entropy immediately after treatment, on par with the CORT group, and in contrast to the control and separate treatment groups. Across the aforementioned biomarkers of the GT and FST, the combination group resembled a mixture of the other groups, which, coupled with a lack of correlations at the short- and long-term time points, hinders the identification of a potential mechanism across time. However, by investigating this interference in the modulation of mPFC activity further, future studies may uncover causal relationships between electrophysiological and behavioral changes.

4.2 Limitations

There are several important limitations to the present study. Sex-based differences were not explored here, though there is evidence of sex-differences in human patients and rodent models of depression (Breslau et al., 1995; Bertholomey et al., 2022). Also, the animals were single housed, which may have altered behavior (Liu et al., 2020). Furthermore, the duration of time immediately post-treatment, 20 min, that was studied here may not have captured all therapeutically-relevant electrophysiological changes induced by the treatments, particularly ketamine (Caixeta et al., 2013). Moreover, without groups that received KET and/or DBS with no CORT, we cannot compare the electrophysiological effects of these treatments in healthy versus stressed brains, limiting the possible interpretations of our data. Finally, due to faulty equipment, weekly SPTs were excluded from the study.

4.3 Conclusion

This study contributes to the growing evidence that electrophysiological measures of the mPFC correlate with behavioral symptoms of depression, as well as the antidepressant action of DBS and ketamine. Therefore, it supports their potential as predictive biomarkers for depression severity and treatment efficacy. Specifically, our study supports previous clinical studies that correlate the exponent and increased inhibition with depression, and is among the first preclinical studies to find a direct correlation between aperiodic-adjusted theta parameters, sample entropy, aperiodic parameters, and depression-like symptoms. For ketamine treatment, our findings support previous studies showing immediate and sustained normalization of mPFC function after ketamine treatment, and novelly demonstrates a correlation between normalization of LFP aperiodic parameters and sample entropy with remission-like behavior after ketamine. This study also supports previous studies demonstrating low gamma parameter modulation and cognitive improvements after mPFC DBS, and is among the first to correlate these measures, as well as sample entropy and aperiodic offset, with remission-like behavior. Finally, this study provides strong evidence that the offset, exponent, and especially sample entropy are potentially universal, cross-modal predictive biomarkers for depression, post-treatment remission, and failed treatment. Further exploration of the mechanisms that interconnect electrophysiological and behavior changes will enable the development of biomarkers for targeted, personalized, and monitored treatment strategies that can address the weaknesses of current treatments. Finally, the complex interaction between the two treatments studied here enhance our understanding of their separate mechanisms and demonstrate that the combination of these treatments may be detrimental to certain aspects of therapeutic efficacy. This needs to be explored further, but the nature of their interaction may be critical information for patients and clinicians.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The animal study was approved by USC Institutional Animal Care and Use Committee. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

MB: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing. SM: Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing. NZ: Conceptualization, Methodology, Project administration, Supervision, Writing – review & editing. LC: Conceptualization, Investigation, Methodology, Software, Supervision, Visualization, Writing – review & editing. JI: Investigation, Writing – review & editing. LD: Investigation, Writing – review & editing. LR: Investigation, Writing – review & editing. EA: Investigation, Writing – review & editing. TL: Investigation, Writing – review & editing. EH: Investigation, Writing – review & editing. WC: Investigation, Writing – review & editing. KW: Investigation, Writing – review & editing. JL: Investigation, Writing – review & editing. DL: Conceptualization, Project administration, Resources, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2024.1389096/full#supplementary-material

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Alterations in electroencephalographic functional connectivity in individuals with major depressive disorder: a resting-state electroencephalogram study

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Background: Major depressive disorder (MDD) is the leading cause of disability among all mental illnesses with increasing prevalence. The diagnosis of MDD is susceptible to interference by several factors, which has led to a trend of exploring objective biomarkers. Electroencephalography (EEG) is a non-invasive procedure that is being gradually applied to detect and diagnose MDD through some features such as functional connectivity (FC).

Methods: In this research, we analyzed the resting-state EEG of patients with MDD and healthy controls (HCs) in both eyes-open (EO) and eyes-closed (EC) conditions. The phase locking value (PLV) method was utilized to explore the connection and synchronization of neuronal activities spatiotemporally between different brain regions. We compared the PLV between participants with MDD and HCs in five frequency bands (theta, 4–8 Hz; alpha, 8–12 Hz; beta1, 12–16 Hz; beta2, 16–24 Hz; and beta3, 24–40 Hz) and further analyzed the correlation between the PLV of connections with significant differences and the severity of depression (via the scores of 17-item Hamilton Depression Rating Scale, HDRS-17).

Results: During the EO period, lower PLVs were found in the right temporal-left midline occipital cortex (RT-LMOC; theta, alpha, beta1, and beta2) and posterior parietal-right temporal cortex (PP-RT; beta1 and beta2) in the MDD group compared with the HC group, while PLVs were higher in the MDD group in LT-LMOC (beta2). During the EC period, for the MDD group, lower theta and beta (beta1, beta2, and beta3) PLVs were found in PP-RT, as well as lower theta, alpha, and beta (beta1, beta2, and beta3) PLVs in RT-LMOC. Additionally, in the left midline frontal cortex-right temporal cortex (LMFC-RT) and posterior parietal cortex-right temporal cortex (PP-RMOC), higher PLVs were observed in beta2. There were no significant correlations between PLVs and HDRS-17 scores when connections with significantly different PLVs (all $p > 0.05$) were checked.

Conclusion: Our study confirmed the presence of differences in FC between patients with MDD and healthy individuals. Lower PLVs in the connection of the right temporal-left occipital cortex were mostly observed, whereas an increase in PLVs was observed in patients with MDD in the connections of the left

temporal with occipital lobe (EO), the circuits of the frontal-temporal lobe, and the parietal-occipital lobe. The trends in FC involved in this study were not correlated with the level of depression.

Limitations: The study was limited due to the lack of further analysis of confounding factors and follow-up data. Future studies with large-sampled and long-term designs are needed to further explore the distinguishable features of EEG FC in individuals with MDD.

KEYWORDS

major depressive disorder, electroencephalography, functional connectivity, phase locking value, neural oscillation

1 Introduction

Major depressive disorder (MDD) is characterized by persistent feelings of sadness, hopelessness, and a loss of interest or pleasure in daily activities; some patients might have recurrent thoughts of death (Marx et al., 2023). According to recent epidemiological data, cases of MDD are estimated to increase to 53.2 million due to the COVID-19 pandemic. The prevalence of people with MDD has increased to 3,152.9 cases per 100,000 population, with disability-adjusted life years (DALYs) reaching 49.4 million, suggesting that MDD, among all mental illnesses, is the leading cause of disability (COVID—Mental Disorders Collaborators, 2021; GBD Mental Disorders Collaborators, 2022). The diagnosis of MDD is mainly based on clinical assessments (including mental state scales or tools), history taking from patients, face-to-face evaluation by psychiatrists, and references to diagnostic criteria or guidelines (American Psychiatric Association, 2022; World Health Organization, 2024). However, the constant presence of subjectivity may influence the accuracy of the diagnosis (Del-Ben et al., 2005). This situation has prompted researchers to explore objective indicators of MDD diagnosis. By doing so, it is possible to avoid the interference of subjectivity in the diagnostic process. Over the years, massive depression-related biomarkers with potential applications in the diagnosis have been discovered (Etkin et al., 2015; Takahashi et al., 2017; Chang et al., 2018; Humphreys et al., 2019; Jones and Nemeroff, 2021), although the range of their applications is relatively narrow and there are still many challenges in their usability, maneuverability, and stability.

Although the pathogenesis remains to be clarified, MDD is considered to be significantly associated with human brains, and more attention has been paid to this area. It has been verified that the emotions of humans can be formed on a scale of hundreds of milliseconds (Hari and Parkkonen, 2015). Electroencephalography (EEG), as a non-invasive, low-cost, and convenient procedure, is quite accessible for detecting valuable brainwave features with high temporal resolution at the millisecond level; thus, EEG has been gradually applied to explore the possibilities of detecting and diagnosing mental illnesses such as MDD (Feldmann et al., 2018). Researchers have developed and applied a variety of analysis methods to identify MDD patients. Mumtaz et al. (2017) differentiated MDD and normal controls using clinical features extracted from EEG. Liao et al. (2017) proposed a method based on EEG signals and a spectral-spatial feature extractor named kernel eigen-filter-bank common spatial pattern, and they achieved an average classification accuracy of 81.23%. Acharya et al. (2015) created a depression diagnosis index by using non-linear features and reported an average accuracy of 98%. Previous findings suggest that some indicators of EEG might be promising biomarkers, while for our current research, functional connectivity (FC) could be the one that shows significant differences.

FC is defined as the temporal correlation among the activities of different neural assemblies; such a correlation originates from statistically significant dependence between distant brain regions. FC mainly reflects the synchronization of two different electrode pairs (Fingelkurts et al., 2005; Sakkalis, 2011). It has been found that FC could be influenced by white matter myelinated cortico-cortical axons as it originates from post-synaptic potentials (Hall et al., 2014; Nunez et al., 2015). Myelin, however, is in charge of the axon, controlling its speed and the synchrony of impulse traffic between different cortical regions, which is fairly important for optimal mental performance (Nunez et al., 2015). Considering that the distances of brain signals are various, it is quite essential to ensure that the signals would reach their target simultaneously, and such a model of connections might explain the wide range of EEG frequency bands (Nunez et al., 2015). There are various measures of FC, including coherence (Han et al., 2021), correlation coefficient, amplitude envelope correlation, phase lag index, weighted phase lag index, synchronization likelihood, and phase locking value (PLV). EEG has been broadly utilized for the analysis of FC in individuals with MDD.

Previous studies have extensively investigated FC in different frequency bands of EEG between individuals with MDD and healthy controls (HCs). For the delta band, a majority of studies did not find any difference (Olbrich et al., 2014; Knyazev et al., 2018; Whitton et al., 2018). Knyazev et al. (2018) reported no difference in FC between individuals with MDD and HCs. Only Leuchter et al.'s study revealed that the FC of individuals with MDD was relatively higher in limited connections (Leuchter et al., 2012). Low connectivity was still observed in individuals with MDD (McVoy et al., 2019; Hasanzadeh et al., 2020). For the gamma band, none of the available findings showed any significant difference between individuals with MDD and HCs (Park et al., 2007; Knyazev et al., 2018; Whitton et al., 2018). For alpha, high-quality studies conducted by Fingelkurts et al. revealed higher FC in individuals with MDD (Fingelkurts et al., 2007; Fingelkurts and Fingelkurts, 2017), whereas FC was observed to be lower in the

findings of Iseger et al. (2017), Knyazev et al. (2018), and Whitton et al. (2018). For the theta band, the results from Fingelkurts's study still showed higher FC in patients with MDD than in HCs (Fingelkurts et al., 2007), but the results of some other studies, such as the findings from Sun et al., presented a completely opposite dynamic (Sun et al., 2019). For beta, most previous studies indicated significant differences between individuals with MDD and HCs, such as the findings from Hasanzadeh et al. (2020), Knyazev et al. (2018), and Leuchter et al. (2012), which revealed relatively higher FC for individuals with MDD. However, some studies reported that patients with depression show lower FC than HCs (Knott et al., 2001; McVoy et al., 2019). Considering the existence of heterogeneity in the method of processing and analysis, as well as the sample sizes that are small or have large differences between groups, more convincing research from the perspective of neurophysiologic is needed, through which we could further discover the essence of pathogenic mechanism in MDD.

Our study focused on the connectivity analysis of resting-state EEG and aimed to observe whether and how the connectivity features of patients with MDD differ from HCs during depressive episodes. We chose to measure PLV, which has been widely used to quantify the correlation between electrodes, to bring deeper insights into the FC and synchronization between different brain regions. As PLV is an indicator containing phase information, it is believed that the measure can reflect FC and synchronization in neuronal activities from the perspective of both time and space. Such spatiotemporal changes can be observed independent of amplitude characteristics. The shift is highly correlated with emotional activity (Cui et al., 2023). In this study, we compared the PLV of EEG in patients with MDD and HCs at different frequency bands and further explored its relationship with the severity of depressive symptoms.

2 Method

2.1 Subjects and participants

The research was conducted among patients admitted at Beijing Anding Hospital, and healthy subjects were openly recruited through advertisement and social media. The study protocol was examined and approved by the Clinical Research Ethics Committee of Beijing Anding Hospital (Registration Number: 2020-106) and complies with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Informed written consent was obtained from all participants or their legal guardians after a complete and extensive description. Inclusion criteria and exclusion criteria were as follows:

Inclusion criteria for participants with MDD: (1) 18–65 years old (including 18- and 65-years-old), regardless of gender. (2) Meeting the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) diagnostic criteria for MDD, and confirmed by the Mini International Neuropsychiatric Interview (M.I.N.I.) 7.0.2, without psychotic symptoms. (3) A Hamilton Depression Rating Scale-17 (HDRS-17) score of $\geq$17. (4) No modified electroconvulsive therapy (MECT) within 30 days prior to enrollment. (5) Elementary school education or above, and the ability to understand the scale. (6) Understanding of the research content and provision of written informed consent.

Inclusion criteria for healthy controls (HCs): (1) 18–65 years old (including 18- and 65-years-old), regardless of gender. (2) No previous or current confirmed diagnosis of mental disorder based on M.I.N.I. 7.0.2 screening. (3) Elementary school education or above, and the ability to understand the scale. (4) Understanding of the research content and provision of written informed consent.

Exclusion criteria for participants: (1) A prior diagnosis of bipolar disorder, schizophrenia, schizoaffective disorder, or mental disorder associated with other illnesses. (2) Previous or current patients of organic brain damage such as epilepsy or other disorders in which random brain discharges are present, or serious physical illnesses that make enrollment in this study inappropriate. (3) Having a history of alcohol or psychoactive substance abuse or dependence within 1 year.

2.2 EEG recording

A Neuracle NeuSen EEG/event-related potential (ERP) Monitor (Neuracle Technologies, Inc., Changzhou, China) connected to a 19-channel EEG cap (Tenocom Medical Technologies, Co., LTD, Qingdao, China) was used to record raw EEG signals. Data were obtained from 19 Ag/AgCl electrode channels using the advanced Neuracle system, which operated at a sampling rate of 1,000 Hz. The 19-channel EEG raw signals included Fp1, Fp2, F3, F4, F7, F8, Fz, T3, T4, T5, T6, C3, C4, Cz, P3, P4, Pz, O1, and O2. While referencing the Cz electrode, we ensured that impedance was maintained below 50 kΩ. The EEG recording was taken in a quiet and confined room, and participants were asked to sit in a comfortable chair, remaining relaxed and awake. During the process, participants were first asked to face a monitor placed 100 cm away with a black background and stare at a white fixation cross located at the central line of sight for 10 min. Then, in the next 10 min, they were required to close their eyes. EEG was recorded during these two periods (eyes-open, EO; eyes-closed, EC). Participants were asked to remain quiet and relaxed, minimizing head and limb movements. Any movement, dozing, or talking/whispering during the process was immediately corrected and accurately recorded.

2.3 Data preprocessing

2.3.1 Preprocessing

The EEGLAB toolbox in MATLAB R2013a was used to preprocess the original EEG data. The steps included the following: Downsampled to 256 Hz and bandpass filtered into 1–40 Hz using a finite impulse response (FIR) filter with a hamming window. The period when the amplitudes were larger than 150 μV was removed. Independent component analysis (ICA) was conducted on the remaining data to extract artificial components, including electrooculogram, electromyography, and electrocardiogram. After calculating the ICA components, the MNE-ICA label (Pion-Tonachini et al., 2019) was used to identify and remove artificial

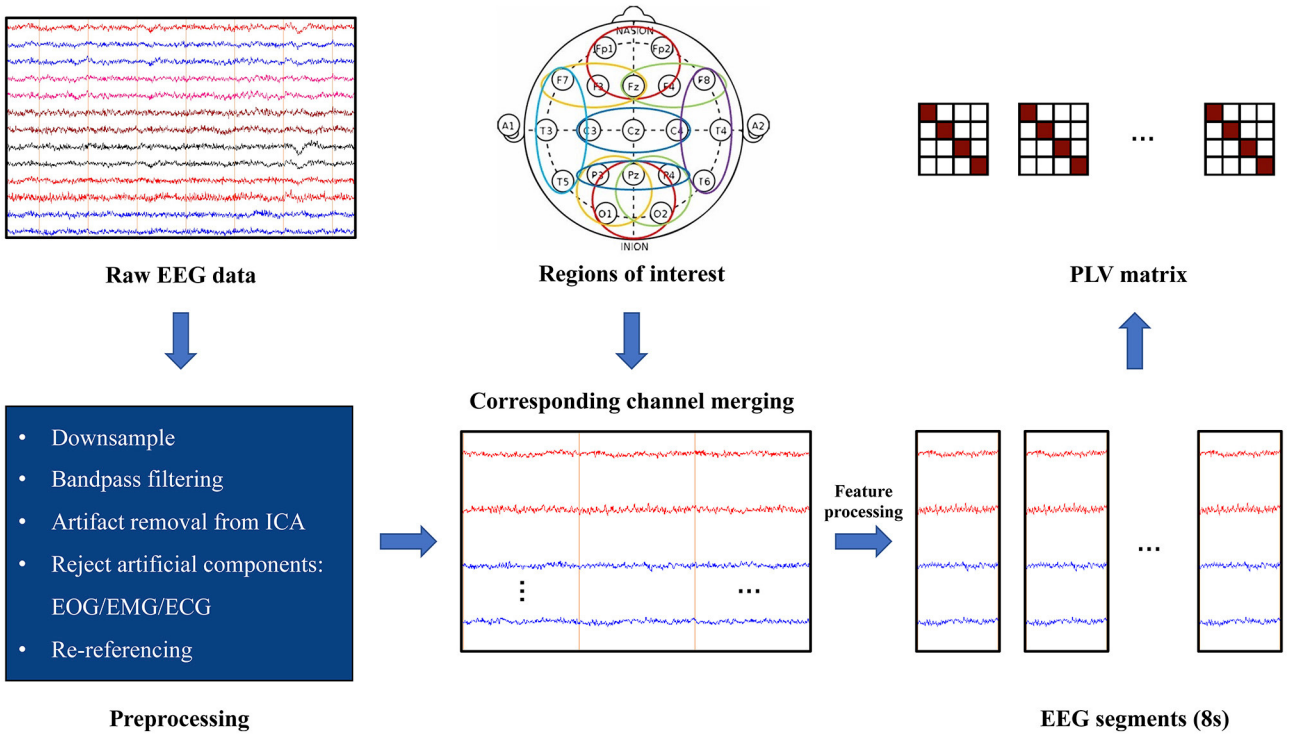

FIGURE 1
Data preprocessing and PLV calculation.

components. The data were then averaged and re-referenced to obtain the preprocessed data (Figure 1).

2.3.2 Feature processing

Based on the findings of previous studies, the following five bands were selected: theta (4–8 Hz), alpha (8–12 Hz), beta1 (12–16 Hz), beta2 (16–24 Hz), and beta3 (24–40 Hz). We utilized existing electrodes to divide brain regions, including prefrontal cortex, PFC (Fp1, Fp2, and Fz); right midline frontal cortex, RMFC (Fz, F4, and F8); left midline frontal cortex, LMFC (Fz, F3, and F7); central cortex, CC (C3, C4, and Cz); parietal cortex, PP (P3, P4, and Pz); left temporal cortex, LT (F7, T3, and T5); right temporal cortex, RT (F8, T4, and T6); midline occipital cortex, MOC (O1, Pz, and O2); right midline occipital cortex, RMOC (P4, O2, and Pz); and left midline occipital cortex, LMOC (P3, O1, and Pz).

Furthermore, feature processing was performed on the data after initial preprocessing (Figure 1): ① The merged signals of each region were filtered into 5 frequency bands by an FIR filter, and then the signal in each band was transformed to a complex signal using the Hilbert transform. ② The mean value of the complex signals of the assigned channels was calculated on each brain region as the signal of that region. ③ They were sliced into pieces (stride: 8s, overlap: 7s). ④ The average mode length (amplitude) of each 8s segment was evaluated: the mode lengths of the signals in three frequency bands were taken and added together. Then, the amplitudes of the signals in all the brain regions were added, and the average over the length of time was calculated. ⑤ Anomalous 8s slices of amplitude were removed.

2.4 FC calculation (PLV)

PLV, as one of the coupling methods for constructing an FC matrix, mainly assesses the significance of the phase covariance between two signals. It depends on the instantaneous phase of signals (Lachaux et al., 1999). First, it requires filtering of the data in the frequency of interest, followed by extraction of the instantaneous phase using the Hilbert transformation. The calculation method was stated as follows:

$$PLV = \left| \frac{1}{N} \sum_{n=1}^{N} \exp\left(i\left[\phi_1(n) - \phi_2(n)\right]\right) \right| \quad (1)$$

In this formula, N represents the length of the time series, and $\phi_1(n)$ and $\phi_2(n)$ separately refer to the instantaneous phase of two signals at time point n (Tan et al., 2022). The process of measure is set up on the assumption of permanent differences between regions, and the PLVs range from 0 to 1 represents the connection strength in a weighted network analysis (Fell and Axmacher, 2011). Figure 2 shows EEG signals with different values of PLV, representing different levels of connection and synchronization in neuronal activities spatiotemporally.

2.5 Symptoms evaluation

The severity of symptoms was assessed with HDRS-17 and the Hamilton Rating Scale for Anxiety (HAMA). The Young Mania Rating Scale was completed by participants at the time

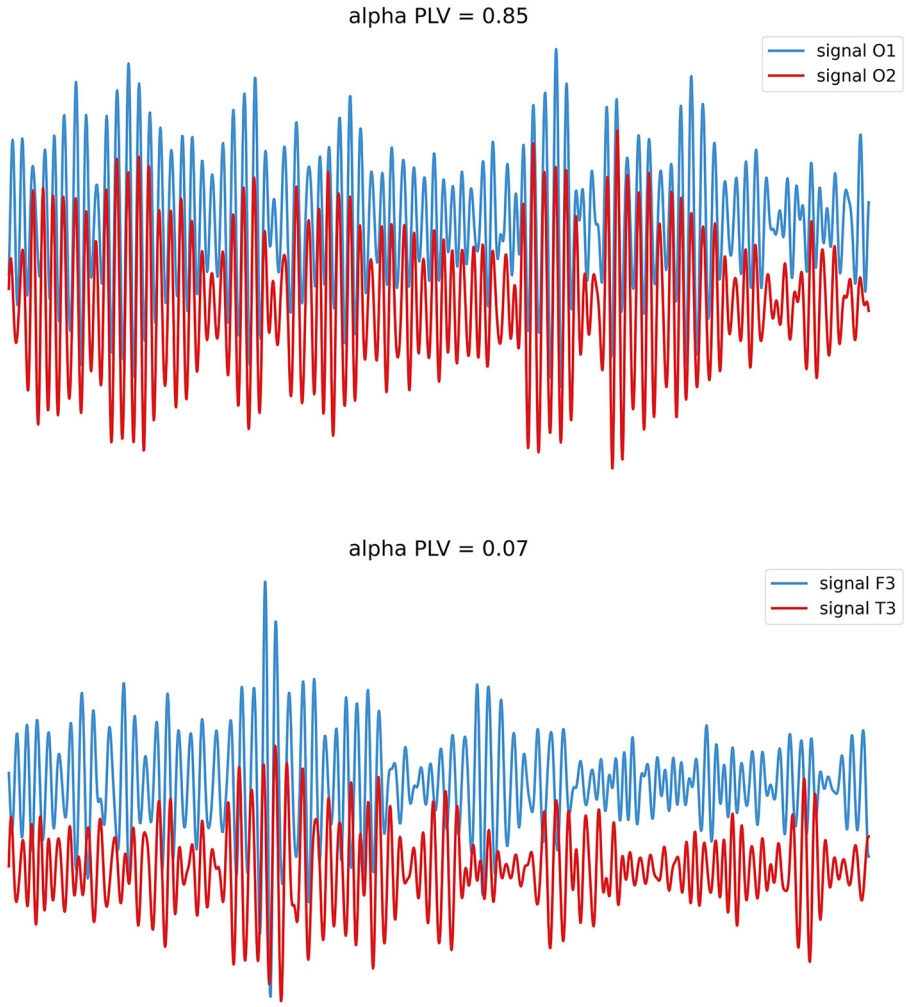

FIGURE 2
EEG with different levels of PLV. Neural oscillations may perform phase synchronization (above; stable phase relationships) or show rare/no phase synchronization (below; variable phase relationships).

of screening, which aimed to exclude subjects with manic or hypomanic episodes.

2.6 Statistical analysis

All data were analyzed using SPSS 26.0 software (IBM, Armonk, NY, USA). Continuous data were tested for normality. Normally distributed continuous data are expressed as mean ± standard deviation (SD), non-normally-distributed continuous data are expressed as median (interquartile range), and categorical data are expressed as n (%). Group differences in continuous data were calculated by conducting a t-test or Mann–Whitney U-test depending on their normality, while for categorical variables, the differences were examined by conducting χ^2 analyses. The relationship between the PLV and HDRS scores was assessed using Spearman's correlation coefficient because of the non-normal distribution of the HDRS data. The significance level in this study was set to 0.05; however, there were multiple comparisons between brain regions, so the Bonferroni method was used to correct the significance of the p-value. The final significance was set to $p < 0.001$ when comparing the connectivity index between the two groups.

3 Results

3.1 Demographic information

The present study was conducted in parallel with Liu et al.'s research, and the socio-demographic information is consistent with that presented in their study (Liu et al., 2024). A total of 169 participants were enrolled in this study, of which 86 were recruited in the MDD group and 83 in the HC group. There was no significant difference in age, gender, current marital status, and education years (all $p > 0.05$). This indicated that the demographic characteristics of the enrolled subjects in the two groups were matched and comparable.

3.2 PLV

We calculated the connections between the 10 brain regions sequentially and compared the MDD group with the HC group.

3.2.1 EO

During the EO phase, there were lower PLVs in the connections of right temporal-left midline occipital cortex (RT-LMOC; theta, alpha, beta1, and beta2) and posterior parietal-right temporal cortex (PP-RT; beta1 and beta2) in the MDD group than those in the HC group. Moreover, PLVs were higher in the beta2 band in the MDD group than those in the HC group when the connections of LT-LMOC were observed (Table 1, Figure 3).

3.2.2 EC

During the EC period, there were lower theta and beta (beta1, beta2, and beta3) PLVs in the connections of PP-RT in the MDD group than those in the HC group. There were also lower theta, alpha, and beta (beta1, beta2, and beta3) PLVs in the connections of RT-LMOC in the MDD group than those in the HC group. Additionally, in the left midline frontal cortex-right temporal cortex (LMFC-RT) and posterior parietal cortex-right temporal cortex (PP-RMOC), higher PLVs were found in the frequency of beta2 (Table 2, Figure 3).

3.3 Correlation analysis

We calculated and statistically correlated the above differential connections' PLVs with the HDRS scores of participants with MDD. The purpose was to verify the relationship between FC and participants' depression levels. After calculation, there were no significant correlations between PLVs and HDRS scores when the connections were examined with significantly different PLVs (all $p > 0.05$).

4 Discussion

In our study, the brain of each participant was categorized into 10 regions of interest according to the orientation of the electrodes. These brain regions cover all parts of the cerebral cortex. We followed this partitioning method to further analyze and compare functional connections between patients with MDD and HCs. The results showed that during the EO period, PLVs of the MDD group were lower than those of the HC group in PP-RT (beta2) and RT-LMOC (theta, alpha, beta1, and beta2), while in LT-LMOC (beta2), the PLVs were higher in the MDD group than in the HC group. During the EC period, PLVs of PP-RT (theta, beta1, beta2, and beta3) and RT-LMOC (theta, alpha, beta1, beta2, and beta3) were found to be lower in the MDD group than in the HC group. However, in the connections of LMFC-RT and PP-RMOC, the PLVs of patients with MDD were demonstrated to be higher than that of HCs in the beta2 band.

We measured and analyzed FC by calculating PLVs in different frequency bands. As mentioned in the introduction, synaptic signals of different frequencies are often linked with top-down inhibitory processes. In EEG studies, these frequencies usually have their own significance in individuals with MDD. Specifically for this research, we analyzed theta, alpha, and beta bands, among which the change in theta and alpha were thought to be the results of white matter dysfunction (Nunez et al., 2015). More specifically, for the alpha band, such violation might disrupt the ability of patients with MDD in terms of attention and executive functions (Miljevic et al., 2023), while for the theta band, the ability of cognitive control could be weakened (Cavanagh and Frank, 2014). Moreover, intrinsically motivated decision-making was associated with the theta and beta bands (Nakao et al., 2012). The following is a discussion and further analysis of our results for the different frequency bands.

4.1 Theta and alpha FC

In past studies, more attention has been given to theta and alpha frequency bands. Most of the studies indicate that resting-state alpha FC is higher in people with depression; more specifically, there are more instances of higher alpha FC in frontal regions and lower FC in the parietal-occipital area. However, for theta bands, there is no consistent conclusion because of the different methods of FC analysis (Leuchter et al., 2012; Ahn et al., 2017; Fingelkurts and Fingelkurts, 2017; Iseger et al., 2017; McVoy et al., 2019; Hasanzadeh et al., 2020; Dell'Acqua et al., 2021; Miljevic et al., 2023). In our study, during EC, FC associated with RT (PP-RT and RT-LMOC) was lower in participants with MDD in the theta band, and alpha FC was also lower in RT-LMOC. For EO, PLVs of RT-LMOC were lower in the MDD group in the theta and alpha bands, which was the same as EC. For alpha, different from previous studies, our findings focused more on the connections of the temporal cortex and occipital area (RT-LMOC). The PLVs of participants with MDD were lower in both EC and EO. It has been pointed out that the temporal lobe plays a crucial role in MDD. Fan et al.'s resting-state functional magnetic resonance imaging (fMRI) study found that aberrant right superior temporal gyrus (STG) activity might be a potential marker of suicide attempts among patients with MDD (Fan et al., 2013). Blackhart et al.'s study indicated that less right parieto-temporal activity is correlated with more severe symptoms of depression (Blackhart et al., 2006). These findings confirm the rationality and validity of our results to a certain extent; abnormal activity in the right temporal lobe may weaken its FC with other brain regions. For the theta band, our results showed lower PLVs in the right temporal-parietal/left occipital region, which has been linked with the decrease of cognitive control efficacy of related top-down processes (Hwang et al., 2015), and lower theta FC was found to be associated with depressive symptoms (McVoy et al., 2019). However, as mentioned before, there are various findings related to theta FC. In the study conducted by Leuchter et al., the resting-state EEG of 121 unmedicated participants with MDD and 37 HCs was included in the analysis. The results showed that the coherences of the participants with MDD were higher than those of HCs between the frontopolar and temporal/parietooccipital regions (Leuchter et al., 2012). Another research that applied phase transfer entropy as the measure of phase-based effective connectivity also indicated

TABLE 1 The differences in EEG PLV between the MDD and HC groups (EO).

		MDD (n=86)	HC (n=83)	Z/t	p
LT-LMOC	beta2	0.188 (0.122, 0.259)	0.133 (0.106, 0.185)	−3.497***	0.000
PP-RT	beta1	0.248 (0.156, 0.364)	0.342 (0.241, 0.459)	−3.509***	0.000
	beta2	0.166 (0.122, 0.274)	0.258 (0.172, 0.397)	−3.739***	0.000
RT-LMOC	theta	0.245 (0.171, 0.343)	0.323 (0.246, 0.448)	−3.755***	0.000
	alpha	0.338 ± 0.136	0.414 ± 0.138	−3.604***	0.000
	beta1	0.333 ± 0.135	0.418 ± 0.132	−4.114***	0.000
	beta2	0.235 (0.152, 0.338)	0.335 (0.247, 0.425)	−4.050***	0.000

Due to data and space limitations, this table presents only the brain region connections where differences were observed.
MDD, major depressive disorder; HC, healthy control; LT, left temporal cortex; RT, right temporal cortex; PP, posterior parietal cortex; LMOC, left midline occipital cortex.
***p < 0.001.

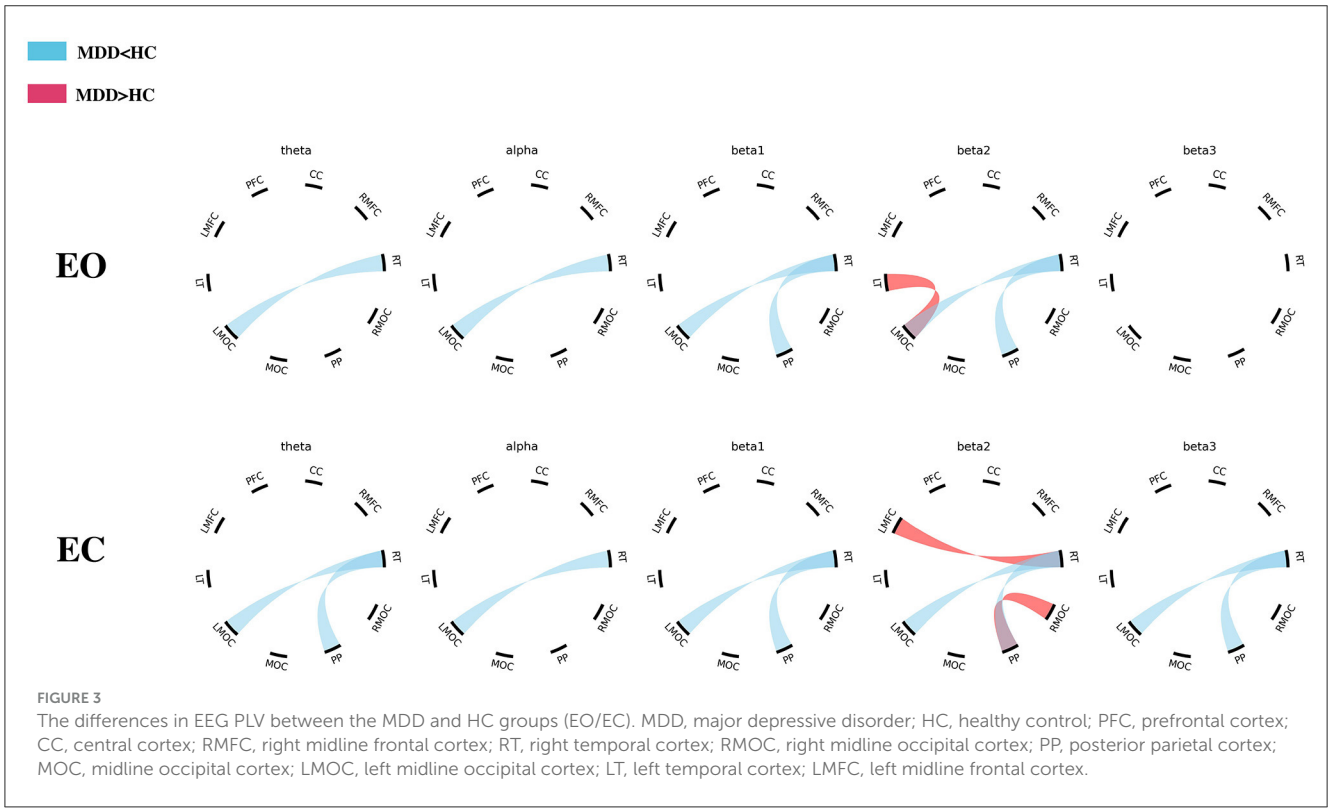

FIGURE 3
The differences in EEG PLV between the MDD and HC groups (EO/EC). MDD, major depressive disorder; HC, healthy control; PFC, prefrontal cortex; CC, central cortex; RMFC, right midline frontal cortex; RT, right temporal cortex; RMOC, right midline occipital cortex; PP, posterior parietal cortex; MOC, midline occipital cortex; LMOC, left midline occipital cortex; LT, left temporal cortex; LMFC, left midline frontal cortex.

a higher node degree and strength in the directed differential connectivity graph (dDCG) of participants with MDD than HCs (Hasanzadeh et al., 2020). Nevertheless, the results of an EEG study among adolescents revealed that the average coherence of the MDD cohort in the theta band was lower than that of HCs; researchers attributed this to the delayed maturation of the default mode network in youth with MDD (McVoy et al., 2019). However, other studies have also found lower theta FC in individuals with MDD. According to the results of Knott et al., patients with MDD exhibited smaller theta coherence values than HCs (Knott et al., 2001). In another pilot study aimed at comparing resting-state EEG coherence in somatic symptom disorder and MDD, researchers found that theta coherence between T5-P3 electrodes (the left temporoparietal junction, which has been linked with cognitive-attentional processing and social interaction) was lower in the MDD group than in the HC group (Ahn et al., 2017). In other words, it is difficult to form a consistent conclusion about the theta frequency band. Future studies with the usage of higher-quality methodological steps are needed to further investigate the differences between individuals with MDD and HCs in theta FC.

4.2 Beta FC

For the beta frequency, there also never seemed to be a consensus. According to a graph theory analysis conducted by Hasanzadeh et al., after calculating the density, degree, and strength of directed dDCG networks in all frequency bands

TABLE 2 The differences in EEG PLVs between the MDD and HC groups (EC).

		MDD (n=86)	HC (n=83)	Z/t	p
LMFC-RT	beta2	0.251 (0.150, 0.330)	0.162 (0.107, 0.267)	−3.774***	0.000
PP-RMOC	beta2	0.742 (0.677, 0.782)	0.695 (0.650, 0.734)	−3.862***	0.000
PP-RT	theta	0.179 (0.145, 0.230)	0.237 (0.183, 0.345)	−4.057***	0.000
	beta1	0.222 (0.163, 0.283)	0.275 (0.213, 0.407)	−3.921***	0.000
	beta2	0.154 (0.117, 0.212)	0.236 (0.170, 0.298)	−5.371***	0.000
	beta3	0.141 (0.096, 0.208)	0.216 (0.151, 0.289)	−4.494***	0.000
RT-LMOC	theta	0.240 ± 0.073	0.302 ± 0.102	−4.482***	0.000
	alpha	0.316 (0.271, 0.382)	0.403 (0.316, 0.477)	−4.006***	0.000
	beta1	0.342 ± 0.102	0.426 ± 0.121	−4.888***	0.000
	beta2	0.289 ± 0.100	0.379 ± 0.119	−5.303***	0.000
	beta3	0.281 ± 0.125	0.376 ± 0.156	−4.401***	0.000

Due to data and space limitations, this table presents only the brain region connections where differences were observed.
MDD, major depressive disorder; HC, healthy control; LMFC, left midline frontal cortex; RT, right temporal cortex; PP, posterior parietal cortex; RMOC, right midline occipital cortex; LMOC, left midline occipital cortex.
***$p < 0.001$.

for normal and MDD groups, the researchers found higher density and strength in beta1 (13–16 Hz). This indicated that there were more links in MDD networks and that their weights were significantly higher than those of the corresponding links in the normal group (Hasanzadeh et al., 2020). Leuchter et al. found higher beta coherence in participants with MDD, primarily in connections within and between electrodes overlying the dorsolateral prefrontal cortical or temporal regions (Leuchter et al., 2012). For the measurement of coherence, another study investigated changes in interhemispheric coherence in different neuropsychiatric disorders. The researchers found that patients with depression showed significantly greater interhemispheric beta coherence in C3-C4 than the control group in both EC and EO conditions (Markovska-Simoska et al., 2018). Different from the results aforementioned, some previous studies stated that the beta FC of participants with depression was lower than that of HCs, such as the study by Knott et al. They compared the coherence measures derived from spectrally analyzed EEGs, and they found that beta coherence was lower in patients with MDD than in HC, regardless of inter-hemispheric or intra-hemispheric differences (Knott et al., 2001). McVoy claimed that beta coherence in adolescents with MDD is significantly lower in the connections of P3-O1 and Fp2-F4; nonetheless, the researcher ascribed the findings to the developmental retardation of the brain (McVoy et al., 2019). In our research, PLVs of beta2 (16–24 Hz) were found to be higher in the region pairs of LT-LMOC (EO), LMFC-RT (EC), and PP-RMOC (EC) in participants with MDD than in HCs, whereas in the connections of PP-RT and RT-LMOC, the FCs were all relatively lower to varying degrees in the beta band. It can be inferred that results presented in the beta band would be diverse depending on their brain area connections. Among beta connections, the frequency of beta2 existed in each connection with significant differences between participants with MDD and HCs. In the study conducted by Huang et al., higher beta2 coherence was observed in participants with MDD than in HCs, including the coherence between the left PFC and right amygdala (F7–T4) and the index between the right PFC and left amygdala (F8–T3; Huang et al., 2023). Looking back at our findings, the PLV of LMFC-RT (EC) was higher in the MDD group than in HCs, which was spatially consistent with the earlier result. However, the previous coherence study was limited to the frontal-limbic circuit, and only a few studies on the beta FC of MDD have focused on specific brain regions; the quality of assessment in these studies also varied. Therefore, considering this and the fuzzy sub-band divisions in the existing studies, further consensus should be reached on methodological steps for obtaining more precise and normatively consistent conclusions.

4.3 The connection of RT-LMOC

We found that in the connection of RT-LMOC, the region pair had lower PLV in almost all the frequency bands, regardless of the EO or EC condition. Previous studies have accustomed us to focus on the FC of a particular electrode pair in a specific frequency band, although witnessing such consistent FC changes was fairly rare. The low functional connection of the right temporal with the left middle occipital region might be one of the critical features of brain dysfunction in patients with MDD. It is known that the temporal lobe contributes to the abilities of language, memory, senses, and emotion, determining how we experience and process certain emotions; the occipital lobe, located at the rearmost position, is mainly responsible for visual processing. More specifically, this part processes visual signals and works collaboratively with other brain regions. It plays a vital role in language and reading, memory storage, and the recognition of familiar objects, such as places or faces. In a meta-analysis study, researchers applied activation likelihood estimation, a method with

ideal spatial sensitivity that can implement voxel-wise statistical comparison of numerous studies, and found that the right STG was the largest among nine significant clusters when analyzing the activation foci associated with happiness. For the same analysis related to greater happiness than sadness, the largest cluster was also located in the right STG, while in the analysis related to greater sadness than happiness, the largest cluster was found in the right middle temporal gyrus.

These results highlighted the significance of the right temporal gyrus in the generation of happy or sad emotions; the lower PLVs of RT-LMOC, which might be a reflection of the process, further established the strong association between depressive mood and the right temporal region (Vytal and Hamann, 2010). An earlier study demonstrated through tractography a direct connection from the extrastriate occipital cortex to the anterior temporal region, as well as indirect connections of the occipital-temporal projection system (Catani et al., 2003). The deficit in these connections might affect the ability to learn novel, non-verbalizable visual stimuli, which is speculated to be the direct way to prime medial temporal structures and facilitate the consolidation of visual memories. This indicated that the lower FC of RT-LMOC might be linked with cognitive dysfunctions in vision-related domains. According to an fMRI study, the middle longitudinal fascicle (MdLF), which is known as the fiber tract that links different parts of temporal lobes, has been validated due to broader connections, including the temporo-occipital region (Makris et al., 2017). Such connections might be related to language, attention, and visual and auditory processing functions; thus, the disruption of the MdLF has been linked with several neuropsychiatric disorders, which might further lead to aphasia, behavioral variants, and attention-deficit disorders. This finding verified the existence of a temporo-occipital connection and its relationship with psychiatric disorders. In our study, the connection of RT-LMOC was found to be weaker in participants with MDD, and the results are consistent with previous findings to a certain extent. However, previous findings were mostly based on the results of cognitive assessments or paradigms in ERP studies, while our study was conducted under resting-state conditions. Thus, future studies must design and utilize some paradigms that can reveal different domains of cognitive functions to further discover the connections of the temporo-occipital region.

4.4 PLV and MDD severity: no correlation

We conducted a correlation analysis between the PLVs of different connections in the two groups and their HDRS-17 scores. The results did not show any significant correlation, which means that the value of PLV could not be determined or that it was immediately affected by the severity of depression. The possible reason might be that FC measured by PLV is more likely to be a persistent trait marker of MDD, indicating that spatiotemporal synchronization between different brain regions could be long-lasting or at least not easily affected and altered soon. As mentioned before, FC is influenced by myelinated cortico-cortical axons of the white matter, and myelin controls the speed of the axon and the synchrony of impulse transportation. This suggests that although FC symbolizes instantaneous phase connection, the changes in PLV are based on physical structure alteration; such alteration might not occur as quickly as MDD becomes more severe or attains remission. Finally, during the period of inclusion, we set the HDRS of participants with MDD as no <17, which means that the patients involved in this study had moderate to severe depression; therefore, the range of scores was relatively narrow when compared to other studies. In future studies, larger-sampled follow-up research is essential to further verify such assumptions. The effect of medical treatment should also be taken into consideration.

4.5 Highlights and limitations

This study is innovative and highlights FC in MDD. In our research, we applied a new classification method of brain regions to demarcate 10 regions of interest and offered a comprehensive and balanced view of the changes in function across different areas of the brain. In terms of FC, different from the connectivity values between electrode pairs, this method of taking the mean value of the assigned channels reflects, to some extent, FC between corresponding brain compartments. In addition, resting-state EEG was observed during the EO and EC phases, which would allow for a broader range of observations because the brainwave patterns of the two states themselves differ in certain frequency bands. This might be due to the different visual sensory information and subjective/objective state characteristics of these two conditions, which might be related to an exteroceptive network and an interoceptive network (Tan et al., 2013; Xu et al., 2014).

Some limitations of this study should be noted. First, although the basic information of the two groups of participants was carefully matched and it was verified that there were no statistically significant differences in the mentioned data, the results of the study are still limited due to the lack of further analysis of some other confounding factors, such as patients' gender, age, and education level. Thus, whether FC was related to these factors could not be determined. Second, we did not further consider the effect of comorbidities, such as anxiety disorders, and their presence might also confound the EEG signals. Finally, as mentioned before, this cross-sectional study lacks follow-up data; whether altered FC is a state marker that can recover after treatment or a persistent trait marker of MDD remains unclear. Large-sampled and long-term controlled studies are still required to further discover the characteristic changes in the EEG of patients with MDD and their relation to the pathogenesis of depression.

5 Conclusions

Compared with healthy individuals, patients with MDD tend to have lower PLV in the connection of the right temporal and left occipital lobes in most cases. However, an increase in PLV can be found in the connection of the left temporal with the left occipital lobe in patients with MDD (EO). During EC, an increase can also be found in the circuits of the frontal-temporal and parietal-occipital regions. The trends in FC observed in this study were not correlated with the level of depression.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Clinical Research Ethics Committee of Beijing Anding Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YW: Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. YCh: Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. YCu: Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – review & editing. TZ: Methodology, Software, Supervision, Validation, Visualization, Writing – review & editing. BW: Data curation, Project administration, Resources, Software, Validation, Visualization, Writing – review & editing. YZ: Formal analysis, Investigation, Software, Supervision, Validation, Writing – review & editing. YR: Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing. SS: Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing. YY: Project administration, Resources, Writing – review & editing. XZ: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing. LZ: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing. GW: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of interest

YCu, TZ, and YY were employed by Gnosis Healthineer Co. Ltd.

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Alpha oscillation mediates the interaction between suicide risk and symptom severity in Major Depressive Disorder

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Objective: The aim of our study was to explore the relationship between changes in neural oscillatory power in the EEG, the severity of depressive-anxiety symptoms, and the risk of suicide in MDD.

Methods: 350 MDD patients' demographic and clinical data were collected, and their depressive and anxious symptoms were evaluated using HDRS-17 and HAMA-14, along with a suicide risk assessment using the Nurses' Global Assessment of Suicide Risk (NGASR). EEG data were captured, processed, and analyzed to study brain activity patterns related to MDD. The participants were divided based on suicide risk levels, and statistical analyses, including chi-square, *t*-tests, Pearson's correlations were used to explore the associations between brain activity, symptom severity, and suicide risk. Closely related variables were identified and ultimately the optimal model was screened using stepwise regression analysis with a forward strategy, and mediation effects were further used to determine the possible interactions between the variables in the regression model.

Results: The regression model showed a significant effect of HDRS-17 and alpha power of Medial Occipital Cortex (MOC) on suicide risk, with elevated HDRS-17 increasing suicide risk and elevated alpha power decreasing suicide risk. Mediation effect analyses showed that MOC alpha power partially mediated the effect of depression level on suicide risk, and that an increase in depression severity may lead to a decrease in MOC alpha power, while a decrease in MOC alpha power may lead to an increase in suicide risk.

Conclusion: The severity of depression directly increases suicide risk, whereas higher alpha power in the MOC serves as a protective factor, reducing this risk. Notably, MOC alpha power not only directly impacts suicide risk but also mediates the effects of both depression severity and anxiety levels on this risk.

Limitations: The relatively small sample size of this study may limit the representativeness of the overall MDD patient population and the detailed analysis of different subgroups. This study did not delve into the relationship between the severity of cognitive symptoms in MDD patients and suicide risk.

KEYWORDS

Major Depressive Disorder, electroencephalography, neural oscillation, suicide risk, intermediary effect

1 Introduction

Major Depressive Disorder (MDD), a leading cause of disability worldwide, significantly impacts individuals' lives through its profound effects on personal well-being, social interaction, and overall quality of life (Greenberg et al., 2021). A cohort study of 158,169 MDD reported 1.4% involved records of suicidal behavior. The all-cause mortality among patients with suicidal behavior was 2.6 times higher than among matched patients with MDD without records of suicidal behavior (Lundberg et al., 2023). The complex interplay between symptom severity and heightened suicide risk in Major Depressive Disorder (MDD) further complicates the clinical landscape. Early suicidal ideation and behavior in MDD are not always apparent in the primary complaint, posing certain difficulties for clinical identification and intervention (Núñez et al., 2020). Consequently, the search for biomarkers related to suicide risk is crucial for early identification and prevention of suicide in MDD.

Studies have shown that certain neurophysiological markers, including specific Electroencephalography (EEG) patterns, can predict suicidal ideation in patients with MDD, providing a potential avenue for identifying at-risk populations (de Aguiar Neto and Rosa, 2019). EEG facilitates the observation of subtle neural oscillation changes, providing insights into the disorder's neurophysiological aspects (Yokoyama and Kitajo, 2022). Abnormal EEG neural oscillations may reflect an imbalance of excitation, inhibition, and hyperactivity in the cerebral cortex of MDD patients. Compared with healthy individuals, MDD showed significantly higher relative power of low delta and theta waves in the right occipital region and significantly lower relative power of α-waves throughout the posterior occipital region (Huang et al., 2023). Dolsen et al. (2017) found increased EEG fast-frequency activity, decreased delta activity, and increased alpha-delta sleep in participants with high suicidal ideation compared to those with low suicidal ideation. The study by Amico et al. investigated the EEG characteristics of suicidal ideation in depressed patients, with a particular focus on resting-state EEG manifestations, and they found that prefrontal EEG imbalances reflected higher anxiety and negative self-references but did not confirm the frequency-specific abnormalities proposed by previous studies in depressed patients (Amico et al., 2023). The study by Jiang et al. showed that decreased beta oscillations in MDD have a key role in promoting suicidal behavior, especially in those MDD patients who have recently attempted suicide, and decreased beta power is associated with increased suicidal behavior (Jiang et al., 2023).

However, current studies have mostly focused on the comparison of EEG characteristics between patients with high and low suicide risk MDD, and the lack of quantitative analyses between depression and anxiety levels, suicide risk and EEG characteristics may explain the heterogeneity between the results of those studies. Our study brings together a comprehensive set of data ranging from basic demographic details to clinical history and psychiatric assessment, combined with the neural oscillatory features of the EEG, with the aim of exploring the mediating role of EEG neural oscillatory features in MDD symptom severity and suicide risk.

2 Method

2.1 Participants

The study was conducted at Beijing Anding Hospital from July 2022 to May 2023. All patients receiving psychiatric services at the hospital during this period were consecutively invited to participate in the survey. The inclusion criteria consisted of age between 18 and 65 years, a diagnosis of MDD according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (Hasin et al., 2018) and a total score of ≥7 on the 17-item Hamilton Depression Rating Scale (HDRS-17). Exclusion criteria included the presence of a severe and unstable medical or surgical condition, a history of alcohol or substance abuse/dependence, and a diagnosis of dementia or other evident cognitive impairments. The study protocol received approval from the Ethics Committee of Beijing Anding Hospital (Registration Number: 2021–86), and all participants provided written informed consent following a thorough explanation of the study details. This study has completed clinical registration on https://www.chictr.org.cn/ (Clinical Trial Registration Number: ChiCTR2200059053).

2.2 Data collection and measurements

The primary socio-demographic and clinical data were collected using a form designed for this study. We collected the basic demographic information of participants, including gender, age, education level, marital status, history of alcohol use, history of tobacco use, family history of mental disorders, body mass index (BMI), number of MDD episodes, duration of MDD and current psychiatric medication. The severity of depressive and anxious symptoms was measured using the HDRS-17 (Hamilton Depression Rating Scale-17 items) and HAMA-14 (Hamilton Anxiety Scale-14 items). These scales are widely recognized in the mental health field for quantifying the severity of depression and anxiety disorders. The HDRS-17 is a 17-item scale that provides a comprehensive assessment of depressive symptomatology, with established validity and reliability in various populations (Kieslich da Silva et al., 2019). The HAMA-14, consisting of 14 items, is specifically designed to assess the severity of anxiety symptoms and has demonstrated sound psychometric properties (Maier et al., 1988). To evaluate suicide risk among MDD patients, we employed the Nurses' Global Assessment of Suicide Risk (NGASR). The NGASR is a standardized assessment tool designed for healthcare practitioners to systematically evaluate and quantify suicide risk in patients. Its selection was based on its practicality in clinical settings and proven efficacy in predicting suicidal behaviors (Cutcliffe and Barker, 2004).

2.3 EEG signal collection and data processing

EEG signal acquisition was meticulously performed, capturing resting-state EEG data from participants through a structured protocol. All participants underwent a 10-min resting state recording with eyes closed and maintain a quiet, alert state. If a participant began to doze off, an auditory warning from the experimenter was issued. Any instances of warnings, opening eyes, or other non-resting states were marked and noted. Upon completion of the experiment, participants were assisted in washing off the conductive EEG paste from their scalp.

Data were obtained from 19 Ag/AgCl electrode channels using the advanced Neuracle system, which operates at a sampling rate of 1,000 Hz. The electrode cap, positioned according to the 10–20 system, utilized the default REF point as the reference electrode during EEG recordings, with impedance consistently kept below 5 kΩ. To control for potential distortion and fluctuations in both noise and signal, we implemented several measures: The EEG recording environment

was carefully controlled for electrical and ambient noise. Participants were prepared adequately to minimize impedance, including skin preparation to reduce resistance. The Neuracle system was calibrated before each recording session to ensure optimal signal acquisition. Continuous monitoring of impedance levels was performed throughout the recording to detect and rectify any deviations promptly. Signal quality was assessed in real-time, with any segments affected by artifacts being marked for exclusion from subsequent analyses.

2.3.1 EEG preprocessing

EEG data preprocessing utilized the EEGLAB toolbox within MATLAB R2013a for bandpass filtering (1–40 Hz), followed by down sampling to 500 Hz. The 10-min EEG dataset was initially segmented into consecutive 120-s intervals, with each of these intervals subsequently divided into 2-s segments. Two-second epochs were employed for artifact rejection and further analysis. Eye movement artifacts were removed by independent component analysis. Epochs with voltage excursions beyond ±150 μV were excluded. Subsequently, data were re-referenced to the average reference, and spectral power and asymmetry were computed for the 2-s epochs.

2.3.2 Power spectrum

Power spectrum analysis was conducted using a Fast Fourier Transform (FFT) algorithm to quantify brain activity in the frequency domain, with power represented by the average instantaneous power of the analytic signal (Han et al., 2021a,b). Relative power for each frequency band was determined by normalizing the absolute power to the total broadband power (Liu et al., 2024), encompassing theta (4–8 Hz), alpha (8–12 Hz), beta1 (12–16 Hz), beta2 (16–24 Hz), and beta3 (24–40 Hz). Electrodes were categorized into 10 regions of interest (ROIs) for focused analysis: Prefrontal Cortex (PFC, including FP1, FP2, and Fz), Right Medial Frontal Cortex (RMFC, including Fz, F4, and F8), Left Medial Frontal Cortex (LMFC, including Fz, F3, and F7), Central Cortex (CC, including C3, C4, and Cz), Parietal Cortex (PP, including P3, P4, and Pz), Left Temporal Cortex (LT, including F7, T3, and T5), Right Temporal Cortex (RT, including F8, T4, and T6), Medial Occipital Cortex (MOC, including O1, Pz, and O2), Right Medial Occipital Cortex (RMOC, including P4, O2, and Pz), and Left Medial Occipital Cortex (LMOC, including P3, O1, and Pz).

2.4 Statistical analysis

Statistical analyses were performed with R version 4.0.3 and MATLAB 2013b. Based on the NGASR scores, we categorized the participants into a low to moderate suicide risk group (NGASR scores ≤8) and a high suicide risk group (NGASR scores ≥9) and made comparisons between the groups. Group comparisons for demographic and clinical variables were conducted using chi-square tests and t-tests, with a significance level set at $p < 0.05$ (two-tailed). Pearson's correlations were used to examine the relationship between neural oscillatory characteristics, symptom severity, suicide risk, and general demographic characteristics. Step-wise linear regression analyses were used to explore independent variables that may have an effect on NGASR in the data of all participants. All variables significantly associated with NGASR were used as independent variables, and the best predictive model was found by adding or removing independent variables stepwise. A forward selection strategy was used to assess the goodness of the model based on the AIC (Akaike Informativeness Criterion) values. *p*-values for stepwise regression analysis and correlation analysis were corrected using False Discovery Rate (FDR). Ultimately, multiple regression analyses were used to explore direct and mediated effects between variables by constructing different regression models. Meanwhile, Bootstrap was used to estimate confidence intervals for the mediating effects to determine whether such effects are significant or not.

3 Results

3.1 Demographic and clinical characteristics of all participants

Data was gathered from 350 patients aged 18–65 (mean age 41.34 ± 14.864), with a gender split of 37.7% male and 62.3% female. The patients had an education range of 5–26 years (average 13.47 ± 3.562 years), and marital status was 32.9% single, 60.0% married, 4.0% divorced, and 3.1% widowed. BMI varied from 14.87 to 48.21 (average 23.93 ± 4.36). Alcohol use was reported by 2.9% and smoking by 9.7%. 76.6% had no family history of mental disorders. The number of depressive episodes was 1–21 (average 3.24 ± 2.80), with MDD duration of 0–40 years (average 7.10 ± 8.17 years). Scores on the HDRS-17 averaged 22.37 ± 5.50, on the HAMA averaged 19.61 ± 7.23, and on the NGASR, 7.05 ± 3.61. Antidepressant usage was 69.4%, antipsychotics 20.9%, mood stabilizers 7.1%, and anxiolytics 27.7%.

Utilizing the NGASR score, we stratified participants into two categories: a low-to-medium suicide risk group (LMS Group; NGASR score ≤ 8, $n = 243$) and a high suicide risk group (HS Group; NGASR score ≥ 9, $n = 107$), and between-group comparisons were made for all variables. NGASR scores were significantly lower in the LMS Group (5.24 ± 2.50) compared to the HS Group (11.18 ± 1.97; $t = -23.856$, $p < 0.001$). HDRS-17 scores were significantly lower in the LMS Group (21.49 ± 5.20) than in the HS Group (24.37 ± 5.66; $t = -4.492$, $p < 0.001$). Similarly, HAMA scores were significantly lower in the LMS Group (18.95 ± 7.21) compared to the HS Group (21.09 ± 7.11; $t = -2.585$, $p = 0.010$). Additionally, The LMS Group exhibited a notably lower BMI (23.52 ± 3.92) compared to the HS Group (24.86 ± 5.13; $t = -2.368$, $p = 0.019$). Antipsychotic medication use differed significantly between the LMS (17.7%) and HS (28.0%) Groups ($\chi^2 = 4.813$, $p = 0.028$). For other factors, including gender, age, education level, alcohol use, tobacco use, family history, marital status, number of episodes, duration of depression, antidepressant use, mood stabilizer use, anxiolytic use, and fluoxetine equivalence dose, there were no statistically significant differences between the two groups on these variables. The dose conversion formula for antidepressants is: fluoxetine 20 mg = citalopram 20 mg = escitalopram 9 mg = paroxetine 17 mg = sertraline 49.3 mg = venlafaxine 74.7 mg = mirtazapine 25.5 mg = agomelatine 26.6 mg = fluvoxamine 71.65 mg = duloxetine 20 mg (Table 1).

Separate between-group comparisons of the relative power of neural oscillations in each frequency band in whole brain regions of the two groups showed that the alpha power in the PFC ($t = 2.23$, $p = 0.026$), RMFC ($t = 2.014$, $p = 0.045$), LMFC ($t = 1.997$, $p = 0.047$), LT ($t = 2.149$, $p = 0.032$), MOC ($t = 2.363$, $p = 0.019$), RMOC ($t = 2.158$, $p = 0.032$), and LMOC ($t = 2.307$, $p = 0.022$) was significantly higher in the LMS Group compared to the HS Group. No significant group differences in relative power of oscillations in other frequency bands (Table 2).

3.2 Correlation analysis

Pearson correlation analyses of demographic information and clinical continuous variables with neural oscillatory power in each frequency band of each brain region were performed in all participants, and the results are shown in Figures 1, 2. NGASR was significantly positively correlated with HDRS-17 and HAMA, respectively (Figure 1). There was a significant positive correlation between HDRS-17 and HAMA, a significant positive correlation between age and BMI, disease duration, HDRS-17, HAMA, a significant negative correlation with education, and a significant positive correlation between disease duration and number of episodes (Figure 1).

NGASR showed negative correlation with alpha oscillatory power of RMOC, LMOC, MOC, LT, PP, and CC, and significant positive correlation with beta3 oscillatory power of RMOC, LMOC, MOC, and PP. HAMA scores were negatively correlated with alpha relative power in RMOC, LMOC,MOC, RT, PP, CC, LMFC, RMFC, PFC, positively correlated with beta3 relative power in RMOC, LMOC,MOC, RT LT, PP, CC, LMFC, RMFC, PFC, and positively correlated with RMOC, LMOC,MOC, RT, LT, PP, CC, LMFC, RMFC, PFC are positively correlated with beta2 relative power. HDRS-17 is negatively correlated with the alpha relative power of RMOC, LMOC, MOC, LT, PP,CC, LMFC, RMFC, PFC, positively correlated with the beta3 relative power of RMOC, LMOC, MOC, RT, LT, PP, CC, LMFC, RMFC, PFC, and positively correlated with the beta2 relative power of RMOC, LMOC, MOC, RT, LT, PP, CC, LMFC, RMFC, PFC LT, PP, CC, LMFC, RMFC, PFC. Age is negatively correlated with beta1 relative power for RMOC, LMOC, RT, LT, PP, CC, LMFC, RMFC, PFC, MOC and positively correlated with beta2 relative power for PP, CC, LMFC, RMFC, PFC, RMOC, LMOC, MOC, RT, LT, PP, CC, LMFC, RMFC, PFC, and BMI is positively correlated with theta relative power of RMOC, LMOC, MOC, RT, LMFC, RMFC, PFC (Figure 2). p values have been adjusted using the FDR correction.

3.3 Regression analysis

Stepwise linear regression analyses were used to explore independent variables that may have an effect on NGASR in the data of all participants. All variables significantly associated with NGASR were used as independent variables, and the best predictive model was found by adding or removing independent variables stepwise. A forward selection strategy was used to assess the goodness of the model based on the AIC (Akaike Informativeness Criterion) values. The final model contained three independent variables: HDRS-17, MOC alpha relative power, and LT alpha relative power. The results showed that the coefficient of HDRS-17 was 0.139 ($t = 4.061$, $p < 0.001$), indicating that HDRS-17 had a significant positive effect on NGASR. The coefficient of MOC alpha relative power was −6.77 ($t = -2.636$, $p < 0.01$), indicating that MOC alpha relative power had a significant negative effect on

TABLE 1 Demographic and clinical characteristics of LMS and HS group.

Characteristics	LMS	HS	Statistics	
	($n = 243$)	($n = 107$)	χ^2/t	p value
Female (%)	150 (61.7)	68 (63.6)	0.105	0.746
Age (years)†	41.73 ± 14.67	40.47 ± 15.33	0.718	0.473
Education level (years)†	13.62 ± 3.40	13.11 ± 3.91	1.110	0.269
Marital status (%)			1.857	0.603
Single	78 (32.1)	37 (34.6)		
Married	150 (61.7)	60 (56.1)		
Divorced	9 (3.7)	5 (4.7)		
Widowed	6 (2.5)	5 (4.7)		
BMI†	23.52 ± 3.92	24.86 ± 5.13	−2.368	0.019
Alcohol use (%)	8 (3.3)	2 (1.9)	0.542	0.462
Tobacco use (%)	23 (9.5)	11 (10.3)	0.056	0.812
Family history (%)	52 (21.4)	30 (28.0)	1.825	0.177
Number of episodes†	3.26 ± 2.91	3.20 ± 2.53	0.218	0.828
Duration of MDD (years)†	6.93 ± 8.13	7.47 ± 8.29	−0.558	0.578
Antidepressant use (%)	175 (72.0)	68 (63.6)	2.508	0.113
Fluoxetine equivalence dose (mg)†	40.84 ± 20.56	38.66 ± 19.56	0.767	0.444
Antipsychotic use (%)	43 (17.7)	30 (28.0)	4.813	0.028
Mood stabilizer use (%)	15 (6.2)	10 (9.3)	1.128	0.288
Anxiolytic use (%)	64 (26.3)	33 (30.8)	0.752	0.386
HDRS-17†	21.49 ± 5.20	24.37 ± 5.66	−4.492	<0.001
HAMA†	18.95 ± 7.21	21.09 ± 7.11	−2.585	0.010
NGASR†	5.24 ± 2.50	11.18 ± 1.97	−23.856	<0.001

†Mean ± SD; HDRS-17: the 17-item Hamilton Depression Rating Scale; HAMA, the Hamilton Anxiety Scale-14.

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TABLE 2 Comparison of relative power between in each frequency band in LMS and HS groups.

Characteristics	LMS (n = 243)	HS (n = 107)	Statistics	
	Mean ± SD	Mean ± SD	t	p value
RMOC_beta3	0.08 ± 0.06	0.09 ± 0.07	−1.706	0.090
LMOC_beta3	0.08 ± 0.06	0.09 ± 0.07	−1.499	0.136
MOC_beta3	0.08 ± 0.07	0.10 ± 0.08	−1.538	0.126
RT_beta3	0.11 ± 0.07	0.12 ± 0.08	−1.11	0.268
LT_beta3	0.12 ± 0.08	0.13 ± 0.09	−1.193	0.234
PP_beta3	0.07 ± 0.05	0.08 ± 0.07	−1.48	0.141
CC_beta3	0.12 ± 0.07	0.13 ± 0.08	−0.807	0.420
LMFC_beta3	0.12 ± 0.08	0.13 ± 0.09	−1.188	0.236
RMFC_beta3	0.12 ± 0.08	0.13 ± 0.09	−1.2	0.232
PFC_beta3	0.11 ± 0.08	0.13 ± 0.10	−1.589	0.114
RMOC_beta2	0.11 ± 0.06	0.12 ± 0.07	−1.293	0.198
LMOC_beta2	0.12 ± 0.06	0.13 ± 0.07	−1.351	0.178
MOC_beta2	0.11 ± 0.06	0.12 ± 0.07	−1.474	0.142
RT_beta2	0.14 ± 0.06	0.15 ± 0.07	−1.321	0.187
LT_beta2	0.14 ± 0.06	0.15 ± 0.07	−1.01	0.314
PP_beta2	0.12 ± 0.07	0.13 ± 0.07	−0.77	0.442
CC_beta2	0.15 ± 0.07	0.16 ± 0.08	−1.116	0.265
LMFC_beta2	0.14 ± 0.07	0.15 ± 0.08	−1.056	0.292
RMFC_beta2	0.14 ± 0.07	0.15 ± 0.08	−1.128	0.260
PFC_beta2	0.13 ± 0.07	0.14 ± 0.08	−0.987	0.325
RMOC_beta1	0.18 ± 0.08	0.18 ± 0.08	0.406	0.685
LMOC_beta1	0.18 ± 0.08	0.17 ± 0.08	0.171	0.865
MOC_beta1	0.17 ± 0.08	0.16 ± 0.07	0.251	0.802
RT_beta1	0.16 ± 0.07	0.16 ± 0.06	0.32	0.749
LT_beta1	0.15 ± 0.06	0.15 ± 0.06	0.598	0.550
PP_beta1	0.19 ± 0.08	0.19 ± 0.08	0.483	0.629
CC_beta1	0.17 ± 0.06	0.16 ± 0.06	0.472	0.638
LMFC_beta1	0.15 ± 0.06	0.14 ± 0.06	1.047	0.296
RMFC_beta1	0.15 ± 0.06	0.14 ± 0.06	1.02	0.308
PFC_beta1	0.15 ± 0.07	0.14 ± 0.06	1.04	0.299
RMOC_alpha	0.44 ± 0.14	0.41 ± 0.16	2.158	0.032
LMOC_alpha	0.44 ± 0.14	0.40 ± 0.15	2.307	0.022
MOC_alpha	0.44 ± 0.14	0.40 ± 0.15	2.363	0.019
RT_alpha	0.39 ± 0.13	0.36 ± 0.15	1.864	0.063
LT_alpha	0.38 ± 0.13	0.34 ± 0.14	2.149	0.032
PP_alpha	0.43 ± 0.14	0.40 ± 0.15	1.776	0.077
CC_alpha	0.36 ± 0.13	0.33 ± 0.14	1.895	0.059
LMFC_alpha	0.37 ± 0.14	0.34 ± 0.15	1.997	0.047
RMFC_alpha	0.37 ± 0.14	0.34 ± 0.15	2.014	0.045
PFC_alpha	0.38 ± 0.14	0.34 ± 0.16	2.23	0.026
RMOC_theta	0.18 ± 0.11	0.19 ± 0.10	−1.239	0.216
LMOC_theta	0.18 ± 0.11	0.20 ± 0.10	−1.319	0.188
MOC_theta	0.19 ± 0.11	0.21 ± 0.10	−1.362	0.174

(Continued)

TABLE 2 (Continued)

Characteristics	LMS (n = 243)	HS (n = 107)	Statistics	
	Mean ± SD	Mean ± SD	t	p value
RT_theta	0.19 ± 0.10	0.20 ± 0.10	−0.951	0.342
LT_theta	0.20 ± 0.10	0.22 ± 0.10	−1.331	0.184
PP_theta	0.18 ± 0.11	0.19 ± 0.10	−1.222	0.223
CC_theta	0.19 ± 0.10	0.20 ± 0.10	−1.32	0.188
LMFC_theta	0.21 ± 0.11	0.23 ± 0.10	−1.461	0.145
RMFC_theta	0.21 ± 0.11	0.23 ± 0.10	−1.394	0.164
PFC_theta	0.21 ± 0.11	0.23 ± 0.11	−1.527	0.128

PFC, Prefrontal Cortex; PP, Parietal Cortex; CC, Central Cortex; MOC, Medial Occipital Cortex; RMFC, Right Medial Frontal Cortex; LMFC, Left Medial Frontal Cortex; LT, Left Temporal Cortex; RT, Right Temporal Cortex; RMOC, Right Medial Occipital Cortex; LMOC, Left Medial Occipital Cortex.

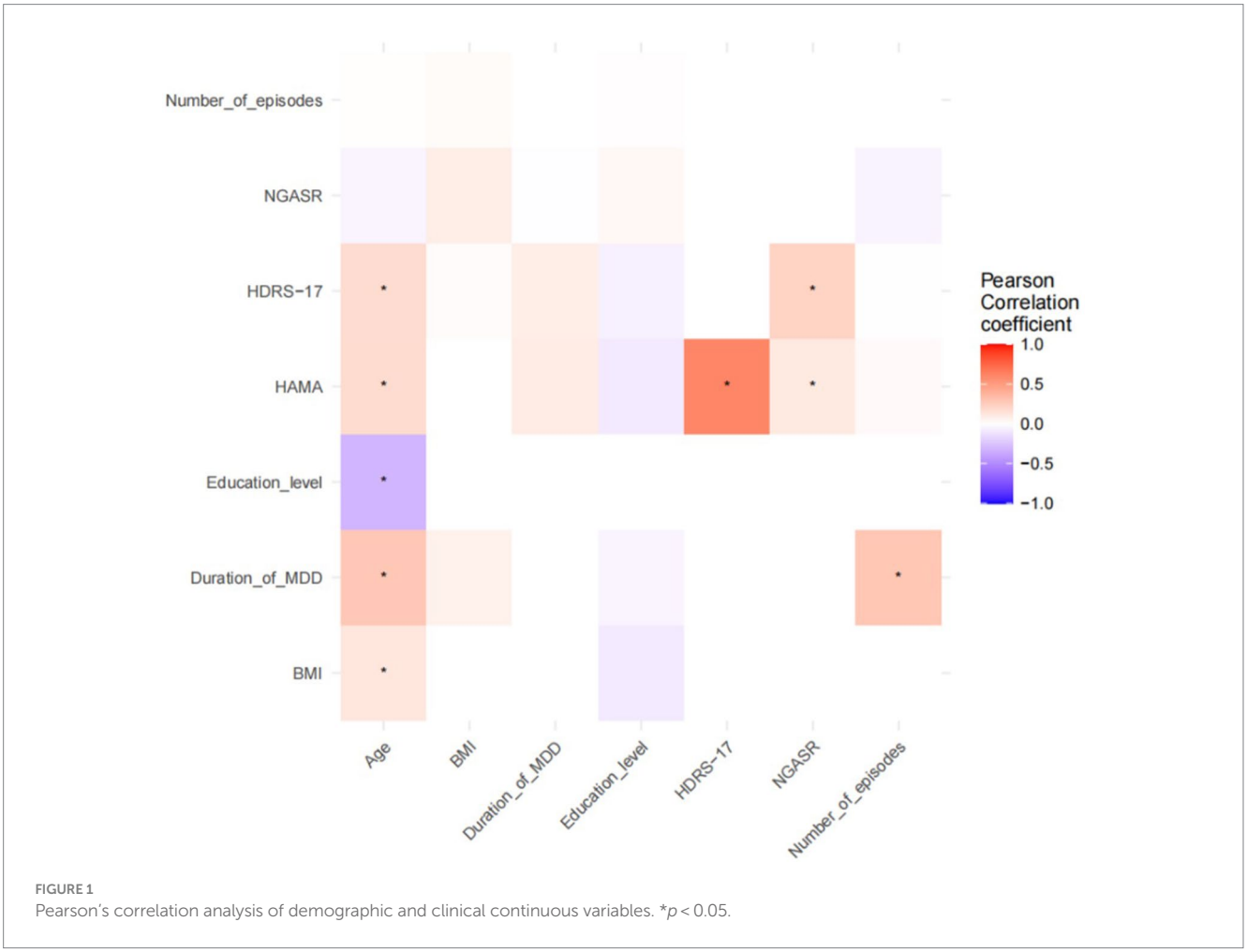

FIGURE 1
Pearson's correlation analysis of demographic and clinical continuous variables. *$p < 0.05$.

NGASR. The coefficient of LT alpha relative power was 4.30 ($t = 1.495$, $p = 0.136$), indicating a statistically insignificant effect of LT alpha relative power on NGASR. p values have been adjusted using the FDR correction.

3.4 Analysis of intermediation effects

The NGASR score was used as the dependent variable, HDRS-17 as the independent variable, and MOC alpha relative power as the mediator variable, and the mediation effect model was constructed based on the percentile bootstrap method, and the results showed that the total effect value of the effect of HDRS-17 scores on the NGASR scores was 0.147 ($p < 0.001$), and the direct effect value was 0.136 ($p < 0.001$) the mediated effect value of MOC alpha relative power was 0.011 (95% BootCI: 0.001 ~ 0.037), with an effect share of 7.316%, and MOC alpha relative power partially mediated the effect of HDRS-17 on NGASR score (Figure 3A).

We further used NGASR score as the dependent variable, HAMA score as the independent variable, and MOC alpha relative power as the

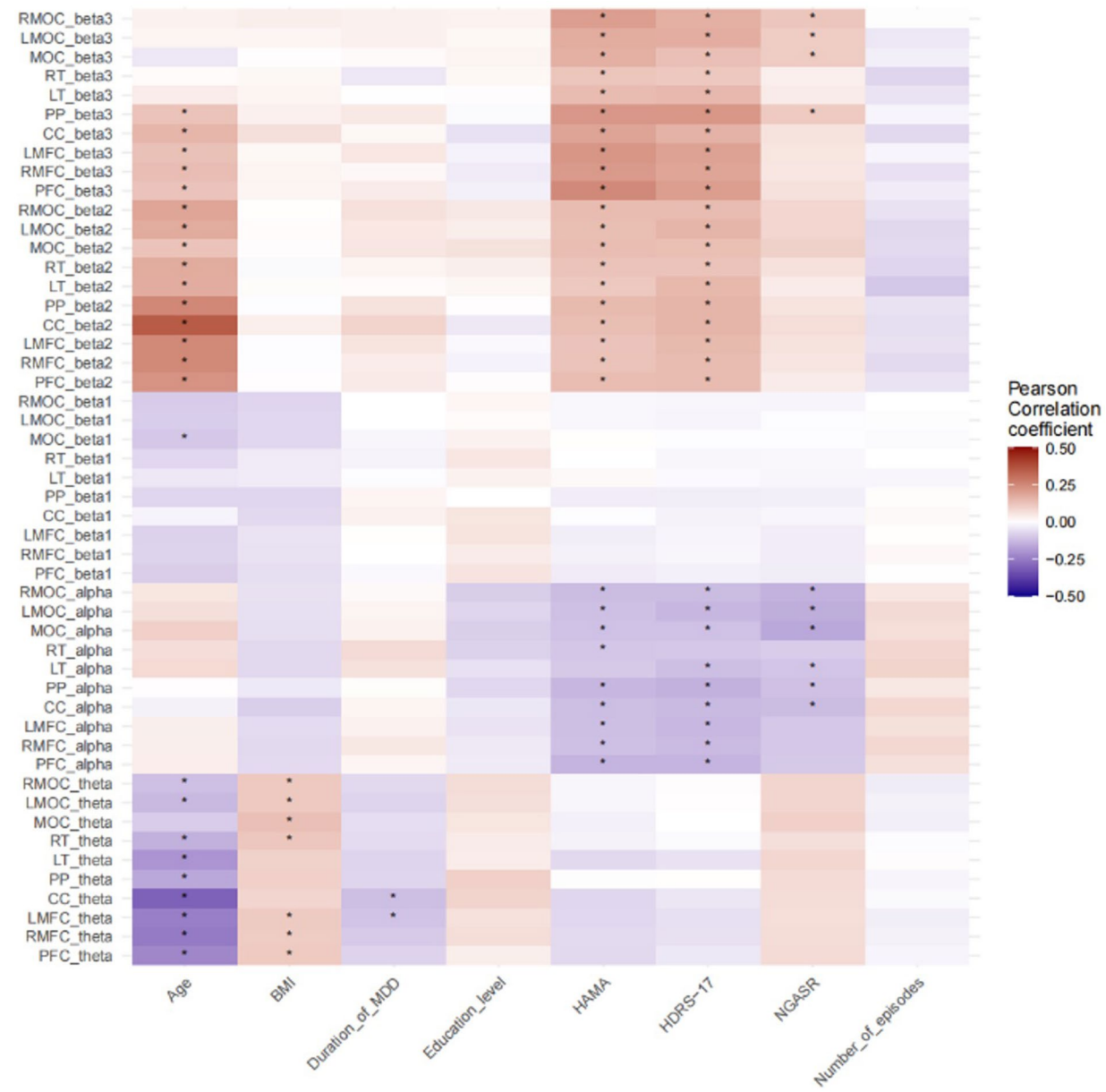

FIGURE 2
Pearson correlation analysis of demographic and clinical continuous variables with neural oscillatory power. *$p < 0.05$; PFC, Prefrontal Cortex; PP, Parietal Cortex; CC, Central Cortex; MOC, Medial Occipital Cortex; RMFC, Right Medial Frontal Cortex; LMFC, Left Medial Frontal Cortex; LT, Left Temporal Cortex; RT, Right Temporal Cortex; RMOC, Right Medial Occipital Cortex; LMOC, Left Medial Occipital Cortex.

mediator variable for mediation effect model construction based on the percentile bootstrap method, and the results showed that the total effect value of the effect of HAMA on the NGASR score was 0.055 ($p = 0.04$), and the direct effect value was 0.046 ($p = 0.084$) the mediated effect value of MOC alpha relative power was 0.009 (95% BootCI: 0.002 ~ 0.042), with an effect share of 100%, and MOC alpha relative power played a fully mediated role in the effect of HAMA on NGASR scores (Figure 3B).

4 Discussion

This study is the first to quantitatively analyses the relationship between suicide risk, depression-anxiety level and EEG neural oscillation power in MDD patients. Our study indicated that higher severity of depression and anxiety is associated with lower alpha power in all brain regions, whereas all brain regions show higher beta2 and beta3 relative power. Suicide risk is negatively correlated with alpha power in multiple brain regions, and positively correlated with beta3 power in specific brain regions. Regression analysis identified HDRS-17 score and MOC alpha relative power as predictors of suicide risk. Mediation effect analyses showed that MOC alpha power partially mediated the effect of depression level on suicide risk, and that increased depression severity may lead to decreased MOC alpha power, while decreased MOC alpha power may lead to increased suicide risk. MOC alpha power fully mediated the effect of HAMA on suicide risk, the magnitude of this effect was small but

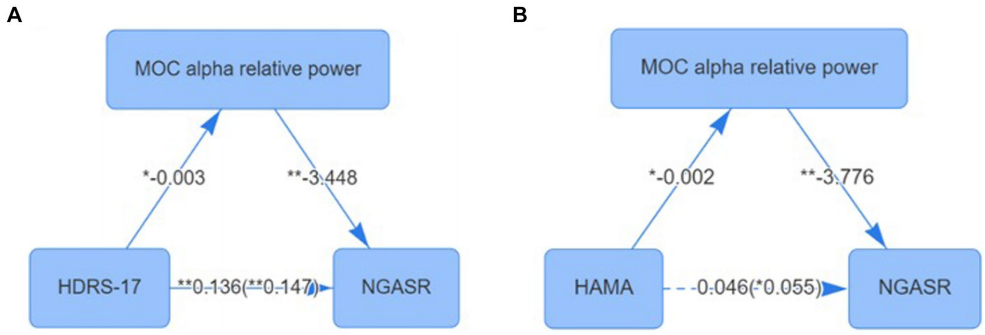

FIGURE 3
(A) Mediating effect of MOC alpha relative power between depression and suicide scores; **(B)** Mediating effect of MOC alpha relative power between anxiety Checked and suicide scores. *$p < 0.05$; **$p < 0.01$; MOC, Medial Occipital Cortex.

statistically significant, and an increase in anxiety may lead to a decrease in MOC alpha power, which may lead to an increase in suicide risk.

The results of the between-group comparisons showed that the severity of depression and anxiety was significantly higher in MDD patients at high suicide risk than in those at low to moderate suicide risk, which is consistent with the results of previous studies (Li et al., 2021). The notably lower alpha oscillation relative power in specific brain regions, including the PFC, LT, and various motor cortex regions (MOC, RMOC, LMOC), in the HS Group compared to the LMS Group is consistent with previous research linking alpha power to the severity of depression and anxiety symptoms (Jiang et al., 2016). Meanwhile, the proportion of antipsychotic use in the medication regimen of depressed patients with high suicide risk was greater than that of those with low to moderate suicide risk, which is closely related to clinical decision-making based on evidence-based medicine (Ruengorn et al., 2012; Nuñez et al., 2022). Many studies have shown an inverse relationship between BMI and suicide, meaning that obese people are less likely to commit suicide than people of low or normal weight (Perera et al., 2016). However, in the sample included in this study, BMI was higher in those with high suicide risk than those with low to moderate suicide risk. This result might be related to the high rate of antipsychotic use in depressed patients at high risk of suicide, which highlighted the intricate relationship between medication regimens, BMI, and suicide risk in MDD patients, emphasizing the need for comprehensive considerations of clinical and pharmacological factors in assessing suicide risk in this population (Hecht et al., 2021).

Based on the correlation analysis results, it is evident that there are significant associations between EEG spectral power, demographic and clinical variables, as well as symptom severity and suicide risk in MDD patients. The positive correlation between NGASR and HDRS-17 as well as HAMA scores underscores the relationship between suicide risk and symptom severity in MDD patients. This finding aligns with previous research indicating that higher depression and anxiety scores are associated with increased suicide risk in individuals with MDD (Conejero et al., 2018; Stanley et al., 2018). Depression and anxiety severity showed a positive correlation with beta2 and beta3 relative power in the whole brain, and a negative correlation with alpha relative power in almost all brain areas. This is consistent with previous studies. Chang and Choi showed that decreases in Alpha/Beta power Ratios (ABR) in central brain areas resulted in increased scores on the Beck Depression Inventory and Spielberg Trait Anxiety Inventory, and that global ABR of the brain are a potentially objective indicator for diagnosing MDD (Chang and Choi, 2023). The overall decrease in ABR may be related to broader changes in functional connectivity during the depressive resting state (Mulders et al., 2015; Helm et al., 2018). Interestingly, NSGAR scores and depression-anxiety severity showed a similar trend of association with alpha and beta oscillatory power, the negative correlation between NGASR and alpha oscillatory power in several brain regions, coupled with the positive correlation with beta3 oscillatory power, which aligns with existing literature suggesting aberrant alpha and beta oscillatory patterns in MDD patients (Dai et al., 2022). It has been suggested that reduced beta1 power moderates the transition from suicidal ideation to suicide in MDD, which may increase the risk of suicide, and the trend of the results of the present study is in line with that (Jiang et al., 2023).

Furthermore, the associations between demographic variables such as age, education, and BMI with specific EEG frequency bands highlight the multifaceted nature of neural oscillatory dynamics in MDD. For instance, the negative correlation between age and beta1 power, and the positive correlation with beta2 power, underscores the impact of age-related changes on neural oscillations, which has been previously documented in the literature (Smith et al., 2023). Similarly, the positive correlation between BMI and theta power aligns with studies linking obesity and altered neural oscillations, indicative of potential neurobiological mechanisms underlying the association between obesity and MDD (Jáuregui-Lobera, 2011).

The results of the regression analysis in our study revealed several significant findings regarding the relationship between EEG spectral power and suicide risk in MDD patients. Specifically, the stepwise linear regression analyses identified HDRS-17 score and MOC alpha relative power as the best predictive model for NGASR. The coefficient of HDRS-17 demonstrated a significant positive effect on NGASR, indicating that depress severe were associated with increased suicide risk. This aligns with previous research highlighting the strong correlation between depressive symptom severity and suicide risk in MDD patients (Martinengo et al., 2019). Furthermore, the relative power of MOC alpha showed a significant negative effect on NGASR, suggesting that lower MOC alpha relative power was linked to elevated suicide risk. This finding is consistent with the notion that aberrant alpha power may reflect disrupted neural activity underlying

emotional dysfunctions in MDD, thus contributing to heightened suicide risk (Umemoto et al., 2021).

A quantitative resting EEG study of Hispanic female adolescents with suicidal ideation and matched normal controls showed that the right hemisphere of normal adolescents had greater alpha (lower activation) than the left hemisphere, whereas suicidal adolescents did not have significant asymmetry in the opposite direction. Alpha asymmetry in the posterior region was associated with the score of suicidal intent, but not with depression severity (Graae et al., 1996), our findings add to those of previous studies. Moreover, our analysis of intermediation effects shed light on the mediating role of MOC alpha relative power in the relationship between depressive symptoms and suicide risk. The mediation effect model indicated that MOC alpha relative power partially mediated the effect of HDRS-17 on NGASR scores, with an effect share of 7.316%. This underscores the potential of MOC alpha relative power as a neurophysiological marker that partially explains the link between depressive symptomatology and suicide risk in MDD patients (Dai et al., 2022). Similarly, the mediation effect model involving the HAMA scores revealed that MOC alpha relative power played a fully mediated role in the effect of HAMA on NGASR scores. This suggests that MOC alpha relative power may serve as a comprehensive indicator of suicide risk, encompassing both depressive and anxiety-related pathways. For instance, a study by Ballard et al. (2022) demonstrated a significant association between decreased alpha power and increased suicidal behaviors in individuals with MDD, highlighting the potential utility of alpha power as a neurophysiological marker for suicide risk assessment.

When discussing the limitations of this study, it is important to acknowledge certain factors that may impact the interpretation and generalizability of the findings. Firstly, the relatively small sample size of this study may limit the representativeness of the overall MDD patient population and the detailed analysis of different subgroups. Larger-scale studies may provide a more comprehensive understanding of the relationship between EEG spectral power dynamics and suicide risk in MDD patients. Secondly, this study did not delve into the relationship between the severity of cognitive symptoms in MDD patients and suicide risk. Cognitive symptoms may play a significant role in MDD patients and could be associated with EEG spectral dynamics (Wang et al., 2024). Therefore, the lack of comprehensive consideration of cognitive symptoms may limit a comprehensive understanding of factors related to suicide risk in MDD patients.

5 Conclusion

The study conclusively demonstrates that among patients with MDD, the severity of depression directly increases suicide risk, whereas higher alpha power in the MOC serves as a protective factor, reducing this risk. The absence of the HAMA in the final regression model suggests a complex interplay of factors influencing suicide risk, potentially moderated by covariance among variables. Notably, MOC alpha power not only directly impacts suicide risk but also mediates the effects of both depression severity and anxiety levels on this risk. This highlights the pivotal role of brain activity patterns, particularly in the MOC, in modulating the relationship between psychological symptoms and the propensity for suicide in individuals with MDD.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Beijing Anding Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

HZ: Data curation, Formal analysis, Investigation, Writing – original draft. XL: Data curation, Formal analysis, Writing – original draft. ZS: Investigation, Methodology, Software, Supervision, Validation, Writing – review & editing. YW: Data curation, Methodology, Visualization, Writing – review & editing. BC: Methodology, Software, Visualization, Writing – review & editing. ZZ: Project administration, Resources, Validation, Visualization, Writing – review & editing. BW: Data curation, Project administration, Resources, Software, Visualization, Writing – review & editing. JZ: Formal analysis, Investigation, Project administration, Resources, Writing – review & editing. LZ: Project administration, Supervision, Writing – review & editing. XZ: Conceptualization, Methodology, Resources, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Sex-specific effects of subchronic NMDA receptor antagonist MK-801 treatment on hippocampal gamma oscillations

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N-methyl-D-aspartate (NMDA) receptor antagonists are widely used to pharmacologically model schizophrenia and have been recently established in the treatment of treatment-resistant major depression demonstrating that the pharmacology of this substance class is complex. Cortical gamma oscillations, a rhythmic neuronal activity associated with cognitive processes, are increased in schizophrenia and deteriorated in depressive disorders and are increasingly used as biomarker in these neuropsychiatric diseases. The opposite use of NMDA receptor antagonists in schizophrenia and depression raises the question how their effects are in accordance with the observed disease pathophysiology and if these effects show a consequent sex-specificity. In this study in rats, we investigated the effects of subchronic (14 days) intraperitoneal injections of the NMDA receptor antagonist MK-801 at a subanesthetic daily dose of 0.2 mg/kg on the behavioral phenotype of adult female and male rats and on pharmacologically induced gamma oscillations measured *ex vivo* from the hippocampus. We found that MK-801 treatment leads to impaired recognition memory in the novel object recognition test, increased stereotypic behavior and reduced grooming, predominantly in female rats. MK-801 also increased the peak power of hippocampal gamma oscillations induced by kainate or acetylcholine only in female rats, without affecting the peak frequency of the oscillations. The findings indicate that blockade of NMDA receptors enhances gamma oscillations predominantly in female rats and this effect is associated with behavioral changes in females. The results are in accordance with clinical electrophysiological findings and highlight the importance of hippocampal gamma oscillations as a biomarker in schizophrenia and depression.

KEYWORDS

electroencephalography (EEG), gamma oscillations, sex-specific, cognition, electrophysiology, ketamine

1 Introduction

N-methyl-D-aspartate (NMDA) receptor antagonists such as ketamine, phencyclidine (PCP) and MK-801 are widely used to pharmacologically model schizophrenia (SZ) in animals (Lee and Zhou, 2019). Beyond that, ketamine and MK-801 show antidepressant effects (Trullas and Skolnick, 1990; Adell, 2020; Johnston et al., 2024) demonstrating that the pharmacology of this substance class is complex.

SZ has a substantial and increasing global disease burden accounting for 1.5% of disability-adjusted life years in the 25–49-year age group (Vos et al., 2020). Although the pathophysiology

of the disease is still not understood, recent genomic studies suggest an association with genes expressed in excitatory and inhibitory neurons in the brain (Trubetskoy et al., 2022). Fine mapping of the associated genes such as the NMDA receptor subunit GRIN2A showed a concentration of the associated genes in pre- and postsynaptic locations (Trubetskoy et al., 2022). These data are in accordance with the postulated interneuron hypothesis of schizophrenia (Lewis et al., 2005) supposing a primary disturbance of the rhythm-generating fast-spiking parvalbumin positive perisomatic inhibitory interneurons (PV INs) in the cortex. The subsequent abnormal local field potential rhythms at gamma and beta frequencies are suggested to be the central pathophysiological trait of schizophrenia, responsible for the negative, positive and cognitive symptoms of the disease (Lee et al., 2003; Lewis et al., 2005). Indeed, increased resting-state and task induced gamma oscillations have been found in patients with schizophrenia (Teale et al., 2008; Donkers et al., 2013; Hirano et al., 2015) and different disease models in animals (Jadi et al., 2016; Speers and Bilkey, 2021) such as acute application of the NMDA receptor antagonist MK-801 (Kehrer et al., 2007; Lemercier et al., 2017). Modulating these oscillatory microcircuits in combination with alternative approaches such as cognitive training and brain stimulation was suggested to represent novel and selective interventions for improving cognition in schizophrenia (Sohal, 2022).

Depressive disorders possess the sixth highest disease burden globally responsible for 3.5% of disability-adjusted life years in the 25–49-year age group (Vos et al., 2020). Although significant advances have been achieved understanding its pathophysiology, no universally accepted mechanism can explain all symptoms of the disease (Otte et al., 2016). Serotonin reuptake inhibitors, the pharmacological backbone of the treatment, are only effective in one-thirds of patients and show therapeutic effects after couple of weeks (Rush et al., 2006). Recently, the focus was shifted to therapeutics with shorter latency such as the NMDA receptor antagonist ketamine. Indeed, while initial models focused on neurochemical changes in the brain, like the monoamine hypothesis, more recent research turned toward a network mechanism to explain the key symptoms of the disease (Spellman and Liston, 2020). Preclinical and clinical data show an overstimulation of NMDA receptors within these dysfunctional neuronal networks (Adell, 2020; Johnston et al., 2024) and that antidepressants have inhibitory effects on NMDA receptors (Szasz et al., 2007). Conforming to this, several studies reported that cortical GABAergic inhibitory circuits and gamma oscillations are impaired in patients with depression or in animal models of the disease and gamma oscillations were suggested as a biomarker for major depression (Mendez et al., 2012; Fitzgerald and Watson, 2018; Liu et al., 2023).

The opposite use of the same substance family in schizophrenia and depression raises the question how the blockade of NMDA receptors changes important biomarkers of these two psychiatric diseases and if these changes are in accordance with the observed disease pathophysiology. Previous studies have investigated the effect of acutely applied NMDA receptor antagonists on cortical gamma oscillations (Kehrer et al., 2007; Lemercier et al., 2017). However, it remained unclear how a long-term administration scheme, as practiced in depressive patients, affects cortical gamma oscillations. Since women are twice as likely to be diagnosed with depression compared to men (Keers and Aitchison, 2010) it is also important to examine whether differences between females and males exist regarding the effects of NMDA receptor antagonists. To shed light onto these questions, the present study was planned to investigate the sex specific effects of chronic application of the NMDA receptor antagonist MK-801 on hippocampal gamma oscillations and its behavioral counterparts. Our results show that subchronic NMDA receptor antagonist administration increased the power of hippocampal gamma oscillations predominantly in females and this change was accompanied with decreased novel object recognition memory and increased stereotypy suggesting that female rats are more sensitive to the effects of the NMDA receptor antagonist MK-801.

2 Materials and methods

2.1 Animals

All procedures were conducted in accordance with the guidelines of the European Communities Council and the institutional guidelines approved by the Berlin Animal Ethics Committee (Landesamt für Gesundheit und Soziales Berlin, G0036/17). Wistar rats were kept in groups of two individuals of same sex and experimental group (treatment or sham group) in one cage. Animals were housed on a 12/12 h light/dark cycle with *ad libitum* food and water. Both sexes of animals from an age of P60 were injected daily for 14 days with an aqueous solution of MK-801 maleate (0.2 mg/kg, 4 male and 4 female rats) in the treatment group or with a sterile 0.9% NaCl solution in the sham group (4 male and 4 female rats). The last i.p. injections were done 24 h before starting the experiments (Figure 1A). While the effects of acute administration of MK-801 on hippocampal gamma oscillations were intensively investigated both *in vitro* (Kehrer et al., 2007; Lemercier et al., 2017) and *in vivo* (e.g., Sullivan et al., 2015), the hippocampal effects of a longer chronic or subchronic application was previously not tested *in vitro*.

2.2 Novel object recognition (NOR) test

The NOR test (Ennaceur, 2010) was carried out according to the protocol by Mathiasen and DiCamillo (2010). Twenty-four hours after the last injection, rats were individually transferred into a separate room and left to acclimatize for 15 min in a resting cage. Before starting the tests, a rat that was not part of the experiment was placed into the test box for 15 min to saturate the box and all objects within with its odor signal. The goal of this was to eliminate exogenous olfactory stimuli in the test box and between objects that would influence the exploration of the objects and their odor-related identification. The experiment was split into two test trials. In the first training trial, two identical objects in standard distance were placed in the test box. The rat was put into the test box for 3 min and recorded on video for the whole time. After 3 min, the animal was removed and put back into the resting cage. One of the objects was exchanged for a novel object. The second test trial started after an intertrial interval of 15 min. The rat was placed for 3 min into the test box and again recorded on video for 3 min. The novel object and side of the novel object within the cage was randomly defined. Animals with no cognitive impairment explore

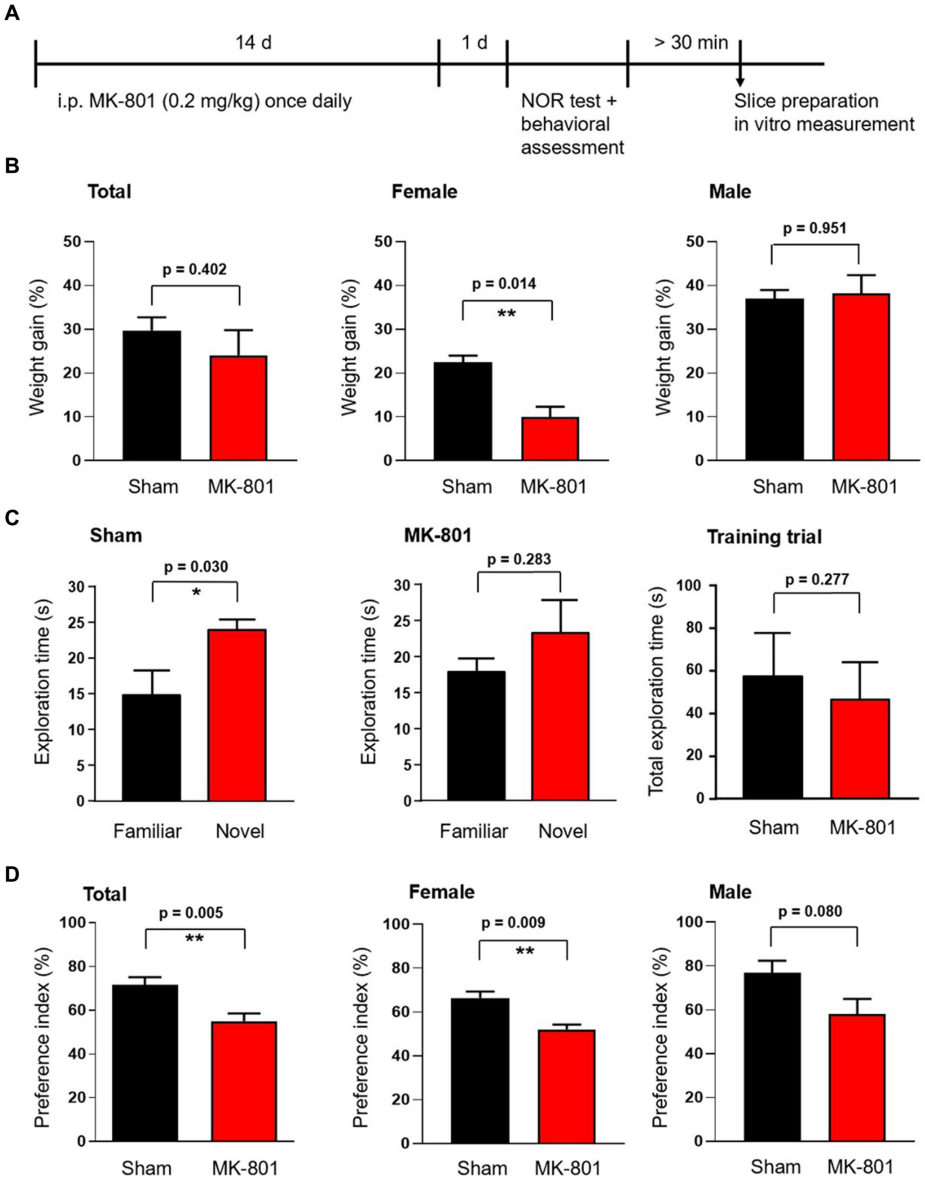

FIGURE 1
Effect of subchronic MK-801 treatment on the novel object recognition memory of rats. **(A)** Overview of the treatment scheme and time points of behavioral and *ex vivo* tests. **(B)** Bar graphs show the weight gain of animals during the 14-days long application of MK-801 (red) or saline (sham, black). Weight gain was significantly reduced in female animals but not in males. **(C)** Bar graphs show the exploration times spent exploring the familiar and novel objects in the novel object recognition (NOR) test. Sham treated rats explored novel objects significantly longer than the already known familiar object (left). MK-801 treatment diminished the difference in exploration time (middle). Sham and MK-801 treated animals explored both (identical) objects in the first training trial similarly (right). **(D)** MK-801 significantly reduced the exploration time spent with the novel object, expressed as novelty preference index (time spent by exploring of the novel object divided by the total exploration time of both objects expressed as percentage, left). The reduction of the preference index by MK-801 was significant in female rats and not in males. Data are mean ± S.E.M, $*p < 0.05$, $**p < 0.01$.

the novel object longer compared to the familiar object. Two independent persons blinded measured the absolute times the rats spent at each object by using the recorded videos. Two parameters were calculated: the exploration time at the objects and the novelty preference index (the time spent by exploring of the novel object divided by the total exploration time of both objects expressed as percentage). Data are presented as mean ± S.E.M. Statistical comparisons of the parameters between sham and MK-801-treated animals were made using Welch t-test. Significance was set at $p = 0.05$.

2.3 Behavioral assessment

For the determination of psychomotor activity, we used the recorded videos of the NOR testing and analyzed them by measuring the duration of time rats spent with three different types of activity during the first trial. First, locomotor activity was defined as the fraction of time (%) during the 3-min test period spent in locomotion. Second, stereotypy was defined as time fraction (%) spent on head-weaving (>2 times side-to-side motion of the head reaching more than 30 degrees from the body axis) or circling (closed loop of locomotion)

or axial turning (circling movements of the forepaws with the haunches remaining still). Third, grooming was defined as the fractional time spent with licking or preening any part of the body (Feinstein and Kritzer, 2013). The sample size was the number of animals. Group size was estimated by the program G*Power3 (Faul et al., 2007). Data are presented as mean ± S.E.M. Statistical comparisons of the parameters between sham and MK-801-treated animals were made using Student's t-test. Significance was set at $p = 0.05$.

2.4 Materials

MK-801, Physostigmine (Physo) and kainate (KA) were ordered from Tocris Bioscience (Bristol, UK). Acetylcholine (ACh) was delivered from Sigma-Aldrich (Taufkirchen, Germany).

2.5 Slice preparation

After the behavioral testing, the rats were transported from the animal house to the preparation room and left for at least 30 min to acclimatize. Afterwards, they were decapitated under isoflurane anesthesia. Their brain was immediately removed and placed in an ice-cold sucrose-based and carbogenated (95% O_2 / 5% CO_2) solution with the following composition (in mM): sucrose, 85; NaCl, 80; $NaHCO_3$, 25; NaH_2PO_4, 1.25; KCl, 2.5; glucose, 25; $CaCl_2$, 0.5; $MgCl_2$, 3. The hemispheres were cut into 400-µm thick horizontal slices containing the formation of the hippocampus by a vibratome (Leica VT 1200S, Leica Mikrosysteme Vertrieb GmbH, Wetzlar, Germany). The slices were immediately transferred to an interface-type recording chamber and constantly perfused with warm (35°C) and carbogenated artificial cerebrospinal fluid (ACSF) with a flow rate of 1.7 mL/min and a composition (mM) of NaCl, 129; KCl, 3; $NaHCO_3$, 21; NaH_2PO_4, 1.25; $MgSO_4$, 1.8; $CaCl_2$, 1.6; glucose, 10. The slices were incubated for at least 30 min in the recording chamber before starting the experiment.

2.6 Recording of gamma oscillations

Gamma oscillations were induced by bath application of either KA (150 nM) or Ach and Physo (10 µM and 2 µM, respectively; Schulz et al., 2012a). Local field potentials (LFPs) were recorded by silver chloride electrodes in micropipettes (ACSF filled, resistance ~3 MΩ) placed in the stratum pyramidale of the hippocampal CA3 area as described previously (Wildner et al., 2024). Recordings were amplified by an EXT-2 (NPI electronic, Tamm, Germany) amplifier, analog low pass filtered at 1 kHz and sampled at 5 kHz by a CED 1401 interface (Cambridge Electronic Design, Milton, UK). For the analysis of pharmacologically induced hippocampal gamma oscillations, power spectra were calculated every 2 min with a 120-s window throughout the recording (Lemercier et al., 2016). From these, the power spectra, peak power, peak frequency, and the quality factor (Q-factor) of the oscillations were determined later by the usage of the Spike2 software. The Q-factor of the gamma oscillations was calculated by the equation: Q = f/B, where f is the peak frequency and B is the bandwidth at 50% of maximum peak power (Meier et al., 2020). Neuronal activity in the power spectrum was considered an oscillation if the Q factor was subcritical (above 0.5) (Lemercier et al., 2017). For the comparison between treated and non-treated groups, the above parameters between 90 and 100 min after gamma oscillation stimulation were compared between slices from MK-801 and sham-treated animals. For the analysis of hippocampal oscillations, a second-order Butterworth band-stop (49.5–50.5 Hz) filter was used to remove 50 Hz noise. Since the power of gamma oscillations is lognormally distributed, peak power (μV^2) is shown as geometric mean with the geometric standard deviation factor (GeoSD) (Klemz et al., 2021) calculated by GraphPad Prism (Boston, MA, USA). Sample size n was defined as individual slices. Group size estimation was done by the program G*Power3 (Faul et al., 2007). The peak frequency (Hz) is represented as mean ± SEM. For the statistical comparisons of the parameters, we used the t-test. The lognormally distributed power values were first log transformed and then statistically analyzed by Student's t-test (Klemz et al., 2022). Significance level was set at $p = 0.05$.

3 Results

3.1 Effects of subchronic MK-801 application on the behavior

To assess the action of MK-801 in female and male rats, we first measured the weight changes of the animals during the subchronic (14 days) application of MK-801 at subanesthetic doses (0.2 mg/kg). During the 2-weeks treatment, MK-801 significantly decreased the relative weight gain of female animals compared to sham-treated controls (10.0 ± 2.3% versus 22.4 ± 1.6%, respectively, $p = 0.006$; $n = 4$ in both groups; Figure 1B). We did not observe the same effect in male animals (MK-801: 38.1 ± 4.2%, $n = 4$; sham: 37.0 ± 1.9%, $p = 0.823$; $n = 4$; Figure 1B).

The novel object recognition (NOR) test is widely used to model recognition memory (Ennaceur, 2010). Sham (saline) treated animals spent in the test trial significantly more time exploring the novel object compared to the familiar object (24.0 ± 1.4 s and 14.7 ± 3.6 s, respectively, $n = 8$, $p = 0.030$; Figure 1C). MK-801-treated animals failed to significantly differentiate between the novel and familiar object and spent comparable time at each (23.3 ± 4.5 s and 17.8 ± 2.0 s, respectively, $n = 8$, $p = 0.283$; Figure 1C). MK-801 might have decreased the novelty preference of the animals because it lowered the object exploration duration in the training trial and herewith the encoding time. To test this possibility we calculated the total exploration times in the training trial in sham and MK-801-treated animals and did not find statistical difference (57.2 ± 7.3 s and 46.4 ± 6.2 s, respectively, $n = 8$, $p = 0.277$, Figure 1C right). Comparing the novelty preference indices (the time spent exploring the novel object divided by the total exploration time in the test trial) revealed that MK-801-treated rats spent significantly less time with exploring the novel object compared to the sham-treated animals ($p = 0.005$; Figure 1D). The sex specific analysis revealed a significant effect of MK-801 only in female rats (66.4 ± 2.9% and 52.0 ± 2.3% in MK-801 and sham, respectively, $n = 4$ in both groups, $p = 0.009$; Figure 1D), while male rats showed only a tendency (76.9 ± 5.5% and 57.9 ± 7.0%, respectively, $n = 4$ in both groups, $p = 0.080$; Figure 1D).

We investigated next the effect of MK-801 on the behavior of the rats and found that MK-801 treatment did not change the locomotor activity of both female and male animals (Figure 2A). In contrast, we observed an increase of the duration of stereotypic behavior from 16.7 ± 1.3% to 24.3 ± 2.0% ($p = 0.006$; $n = 8$ in both groups, Figure 2B). This increase was only observed in female rats (from 17.8 ± 0.5% to 29.0 ± 1.5%, $p = 0.0004$) and not in males (15.5 ± 2.7% vs. 19.5 ± 1.1%, $p = 0.217$; Figure 2B). Measuring the time rats spent with grooming revealed a significant decrease from 10.5 ± 2.9% to 1.9 ± 1.1% ($p = 0.009$, $n = 8$) without an observed sex difference (Figure 2C).

In summary, subchronic low and subanesthetic application of MK-801 had a significant behavioral effect characterized by a reduced weight gain during the 14 days of treatment, an impaired novel object recognition, increased stereotypic behavior and decreased grooming, predominantly in female animals.

3.2 Effects of subchronic MK-801 on *in vitro* hippocampal gamma oscillations

Local *in vitro* gamma oscillations can be induced pharmacologically by activation of KA and muscarinic receptors (Fisahn et al., 1998, 2004). Because these gamma oscillations are probably generated by different networks (Bartos et al., 2007) and can be modulated differentially (Schulz et al., 2012b) we tested the effects of MK-801 administration on both variants. The peak power of KA-induced gamma oscillations in hippocampal slices from female and male sham-treated rats did not differ (geometric mean, geometric SD factor: 18.7 μV², 31.4 μV², $n = 22$ and 26.5 μV², 35.8 μV², $n = 15$, respectively, $p = 0.891$; Figure 3B). MK-801 treatment significantly increased the peak power (geometric mean, geometric SD factor: 21.5 μV², 31.7 μV², $n = 37$ and 109.8 μV², 8.3 μV², $n = 32$, respectively, $p = 0.019$; Figures 3A,Ca). When analyzed for sex-specific effect, we observed an increase of power only in female rats (sham: geometric mean, geometric SD factor: 18.7 μV², 31.4 μV², $n = 17$; MK-801: 197.7 μV², 4.5 μV², $n = 22$; $p = 0.007$; Figure 3Cb) while in male animals MK-801 did not have an effect (sham: geometric mean, geometric SD factor: 26.54 μV², 35.84 μV², $n = 15$; MK-801: 56.39 μV², 12.82 μV², $n = 15$, respectively, $p = 0.555$; Figure 3Cc). We observed neither difference or sex-specific effects in the peak frequency of the induced gamma oscillations from sham and MK-801 treated animals (33.7 ± 0.8 Hz and 34.3 ± 0.9 Hz, respectively, $p = 0.614$; Figure 3D).

Next, we induced gamma oscillations in hippocampal slices with ACh (10 μM) and Physo (2 μM). The peak power values did not differ in sham treated female and male rats (geometric mean, geometric SD factor: 7.7 μV², 8.8 μV², $n = 19$ and 22.2 μV², 13.0 μV², $n = 15$, respectively, $p = 0.238$; Figure 4B), similar to findings in mice (Guneykaya et al., 2023). Subchronic treatment with MK-801 increased the power of cholinergically induced gamma oscillations (geometric mean, geometric SD factor: 44.0 μV², 5.6 μV², $n = 29$) compared to sham treatment (13.9 μV², 11.6 μV², $n = 35$; $p = 0.031$; Figures 4A,Ca). The effect of MK-801 was stronger in female animals compared to males, although it did not reach the significance level (sham: geometric mean, geometric SD factor: 9.8 μV², 10.7 μV², $n = 20$; MK-801: 34.1 μV², 6.1 μV², $n = 14$; $p = 0.091$; Figure 4Cb). In male rats, MK-801 did not increase the power (sham: geometric mean, geometric SD factor: 22.2 μV², 13.0 μV², $n = 15$; MK-801: 56.0 μV², 5.3 μV², $n = 15$, respectively, $p = 0.253$; Figure 4Cc). MK-801 treatment did not affect the peak frequency of the oscillations (sham: 37.0 ± 0.8 Hz, $n = 35$ and MK-801 36.7 ± 0.8 Hz, $n = 29$, respectively, $p = 0.765$; Figure 4D) and we did not observe a sex-specific effect of MK-801 on the peak frequency (not shown).

Thus, subchronic MK-801 treatment increased the power of both KA- and acetylcholine induced gamma oscillations in the hippocampus. KA-induced gamma oscillations were clearly sex-specific and significantly increased only in females rats. Cholinergic gamma oscillations showed only a tendency for sex-specificity.

4 Discussion

The aim of this study was to evaluate the effects of subchronic application of the NMDA antagonist MK-801 on the behavior and hippocampal local network activity in rats. We found that a 14-day subanesthetic treatment with MK-801 enhanced the amplitude of hippocampal gamma oscillations. This effect was seen predominantly in female animals and was associated with increased stereotypy, decreased grooming and impaired recognition memory.

Gamma oscillations reflect rhythmic neuronal network activity that is synchronized across neurons and brain areas (Buzsáki and Wang, 2012). They can be registered by scalp electroencephalography (EEG), electrocorticography, magnetoencephalography or by measuring local field potentials (LFPs) intracranially in the brain tissue. In addition, since gamma oscillations are generated locally by an interplay between pyramidal cells and parvalbumin positive interneurons (Hájos and Paulsen, 2009) it is possible to induce and measure them *ex vivo* in acutely isolated brain slices by means of LFP measurements (Fisahn et al., 1998; Schulz et al., 2012b). Pharmacologically induced *ex vivo* gamma oscillations in the CA3 were shown to correlate with *in vivo* neuronal activity and space reference memory (Lu et al., 2011) confirming that they are a useful measure of *in vivo* network activity and associated behavior in brain slices offering the advantage of investigating real local processes.

Gamma oscillations are proposed to coordinate fundamental neuronal processes underlying cognition (Fries, 2009) and have been associated with higher cognitive functions such as perception, attention, learning and memory (Bosman et al., 2014). In the hippocampus, they play a role in working memory (Yamamoto et al., 2014), in memory replay (Carr et al., 2012) as well as in novel object recognition (Trimper et al., 2014, 2017). The novel object recognition test is widely used to model recognition memory (Ennaceur, 2010). The hippocampus operates as a novelty detector comparing incoming and stored information which might be a key function of exploratory behavior during discovering the environment (Honey et al., 1998; Johnson et al., 2012). The hippocampus is involved in the novel object recognition memory when a delay longer than 10 min is entailed between the first and the second trials of NOR (Cohen and Stackman, 2015). Our results, using 15 min delay between the trials, showed that MK-801 affected both hippocampal gamma oscillations and NOR, including the predominant effect in female animals. This suggests that the increased power of hippocampal gamma oscillations is associated with the impaired recognition memory.

While gamma oscillations play a key role in cognition, their malfunction was observed both in schizophrenia and depressive disorders. In schizophrenia patients, baseline resting-state and

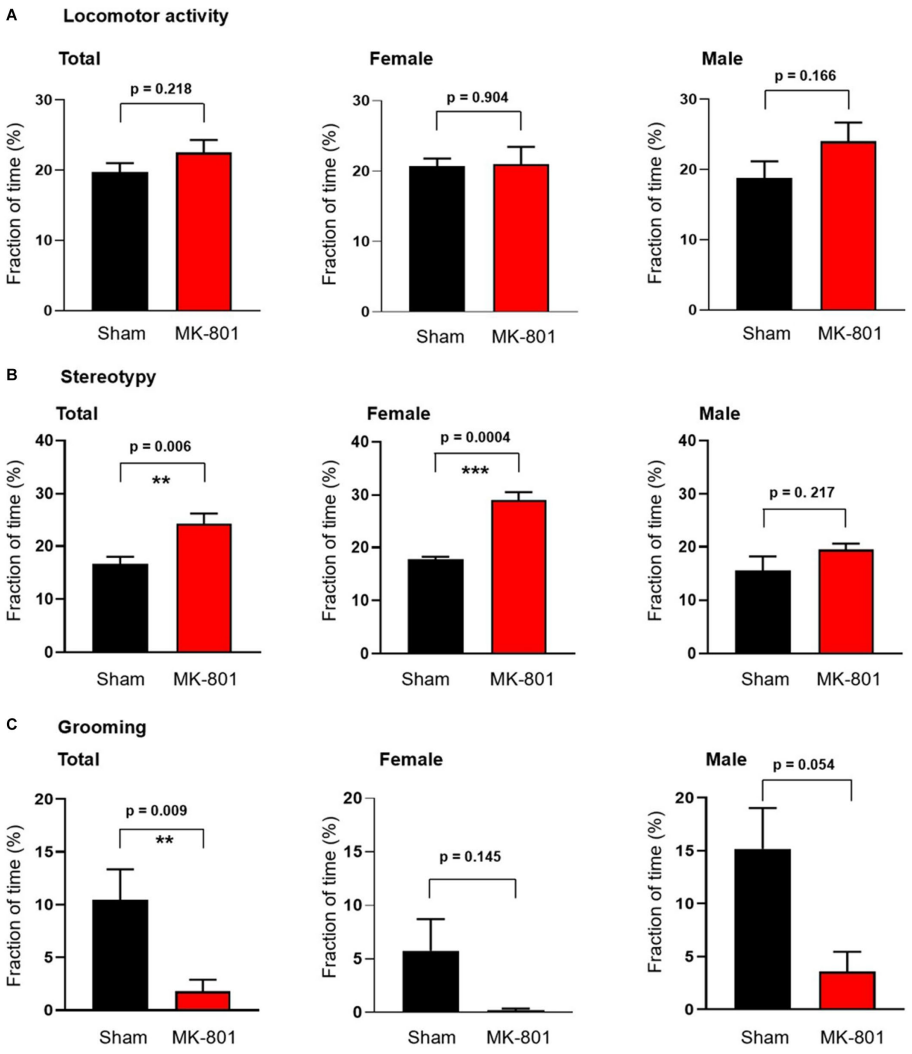

FIGURE 2
Sex-specific behavioral effects of subchronic MK-801 treatment. **(A)** MK-801 had no effect on the locomotor activity. **(B)** 14-day long treatment with MK-801 increased stereotypy in female animals but not in males. **(C)** MK-801 decreased grooming behavior. Data are shown as mean ± S.E.M, $^{**}p < 0.01$, $^{***}p < 0.001$.

task-induced gamma oscillations are increased similar to gamma oscillations in animal models (Teale et al., 2008; Donkers et al., 2013; Hirano et al., 2015; Lemercier et al., 2017; Hasam-Henderson et al., 2018). On the contrary, steady-state gamma responses evoked by repetitive sensory, in most cases auditory stimuli are decreased in both patients and animals studies (Sivarao et al., 2013; Thuné et al., 2016; Choi et al., 2023). While the power of induced gamma oscillations correlated with cognitive performance (Johannesen et al., 2016; Perrottelli et al., 2022) most studies reported no significant associations between the steady state gamma response and cognition in schizophrenia patients (Light et al., 2006; Kirihara et al., 2012; Perrottelli et al., 2022). An explanation for the opposing change of gamma oscillation power could be that pathologically increased baseline gamma power preceding the trial might limit the ability of bottom-up sensory transmission evoked gamma activity to further increase. This might impede the encoding of new information leading to reduced trial accuracy (Johannesen et al., 2016). We modeled the disease with a 14-day long i.p. application of 0.2 mg/kg MK-801 to adult rats. In contrast to single dose NMDA antagonist applications modeling acute first episode schizophrenia (Kehrer et al., 2007; Sullivan et al., 2015; Lemercier et al., 2017) the longer application is supposed to simulate a chronic disease state in animals (McNally et al., 2013). To test the effect of MK-801 on the behavior we analyzed the locomotor activity, stereotypy and grooming of the of the animals. While hyperlocomotion and stereotypy are considered as surrogates for the positive symptoms of schizophrenia, reduced grooming models the negative signs (Feinstein and Kritzer, 2013). In our experimental setup, subchronic treatment with MK-801 increased stereotypy only on female rats, in line with previous studies showing more pronounced effects in this sex (Hönack and Löscher, 1993; Andiné et al., 1999; Devaud, 2003). Subchronic MK-801 treatment did not significantly suppressed grooming in females which is in agreement with earlier findings after acute application (Feinstein and Kritzer, 2013). Although a profound hyperlocomotor activity was observed after acute application of MK-801 in females (Feinstein and Kritzer, 2013), we did not observe a treatment effect after subchronic

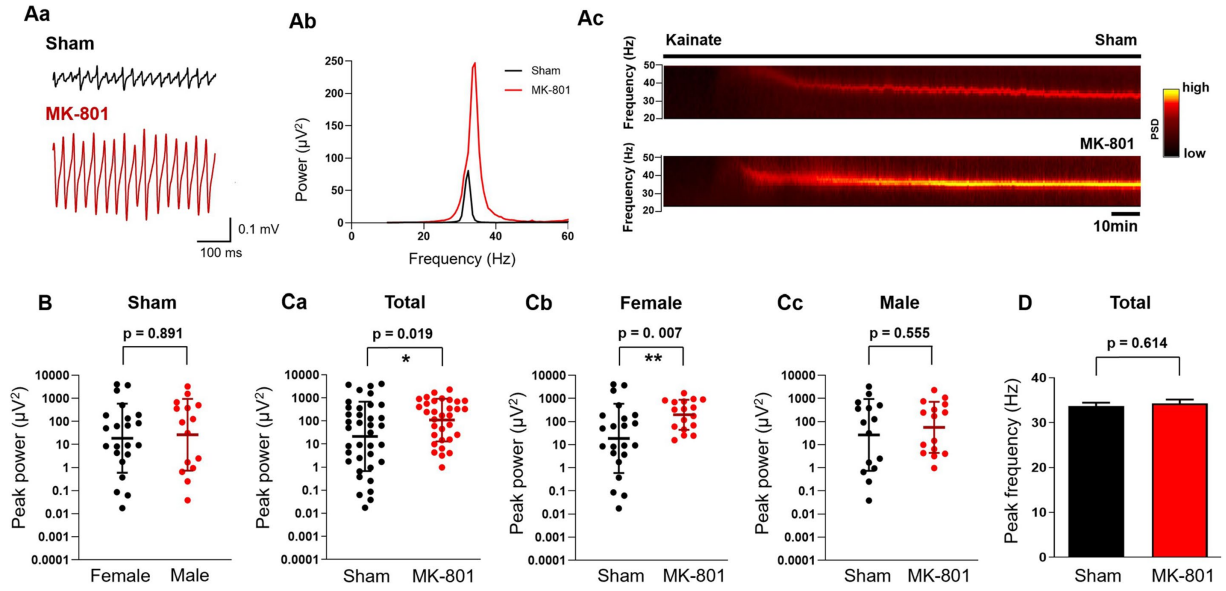

FIGURE 3
Subchronic MK-801 treatment increased the power of *ex vivo* gamma oscillations induced by bath application of kainate (KA). **(Aa)** Representative local field potential traces in hippocampal CA3 slices of sham and MK-801 treated rats after the application of KA (150 nM). **(Ab)** Representative power spectra of KA-induced hippocampal gamma oscillations from sham (black) and MK-801 (red) treated animals. **(Ac)** Representative spectrograms from sham (black) and MK-801 (red) treated animals. Horizontal bar indicates the duration of KA application. **(B)** Scatter plots of the peak power of KA-induced gamma oscillations in female (black) and male (red) sham treated animals. Bars indicate geometric mean and geometric standard deviation factor. **(Ca)**: MK-801 (red) increased the peak gamma power compared to sham (black) treated animals. Bars indicate geometric mean and geometric standard deviation factor. MK-801 (red) increased the peak power of gamma oscillations compared to sham (black) treatment in female rats **(Cb)** but not in males **(Cc)**. Bars indicate geometric mean and geometric standard deviation factor. **(D)** MK-801 did not affect the peak frequency of gamma oscillations. PSD, Power spectral density; $*p < 0.05$, $**p < 0.01$.

MK-801 application presumably because the induction of stereotyped behavior counteracted ambulatory activity (van den Buuse, 2010). The results suggest that subchronic application of MK-801 daily induced a behavioral phenotype in the treated rats resembling both positive and negative symptoms of schizophrenia.

Present study investigated for the first time the effect of subchronic MK-801 on *ex vivo* pharmacologically induced hippocampal gamma oscillations. While the effects of acute systemic application of MK-801 on hippocampal gamma oscillations was intensively investigated in animal studies both *in vitro* (Kehrer et al., 2007; Lemercier et al., 2017) and *in vivo* (e.g., Sullivan et al., 2015; Cui et al., 2022), a longer application was previously not tested *in vitro* in the hippocampus. In prefrontal cortex slices, five-day-long MK-801 application decreased the power of gamma oscillations (McNally et al., 2013). *In vivo* measurements from the hippocampus of rats showed no effects of a 21-day-long MK-801 treatment on the hippocampal gamma (Sullivan et al., 2015). We found that MK-801 increased the gamma power in hippocampal slices indicating that *ex vivo* induced gamma oscillations response to systemic MK-801 application similar to baseline resting-state and task-induced gamma oscillations measured in schizophrenia patients. Our results suggest that modeling schizophrenia with systemic application of an NMDA receptor antagonist and the subsequent registration of pharmacologically induced *ex vivo* gamma oscillations in the hippocampus reproduces electrophysiological traits found in patients and can used as a biomarker for further research and pharmacological testing.

NMDA receptor antagonists, on the other hand, are used in the treatment of depressive disorders. Recent studies described reduced resting-state pre-task gamma oscillations in patients (Pizzagalli et al., 2006; Wang et al., 2023), and emotional task induced and steady-state evoked gamma oscillations were also found to be impaired (Lee et al., 2010; Liu et al., 2014, 2023). Animal models of depression induced with chronic unpredictable mild stress showed decreased auditory steady-state gamma responses (He et al., 2023). In last years, gamma oscillations have been increasingly suggested as a novel biomarker for major depression (Fitzgerald and Watson, 2018; He et al., 2023; Liu et al., 2023). Our results indicate that a longer application of the NMDA receptor antagonist MK-801 significantly increases the power of gamma oscillations suggesting that pharmacological treatment with an NMDA antagonist might normalize the reduction of the power observed in both patients and animal models. These findings are in line with experiments showing that memantine, an NMDA receptor antagonist used in the treatment of Alzheimer's disease, also increased the power of hippocampal and neocortical gamma oscillations (Guadagna et al., 2012; Ahnaou et al., 2014; Ma et al., 2015).

The mechanism behind the increased gamma power after NMDA receptor antagonism currently remains unknown, however, two main hypotheses are considered to play a role: the theory of direct inhibition of cortical pyramidal cells and the disinhibition theory (Miller et al., 2016). The direct inhibition hypothesis postulates that an antagonism of extrasynaptic NMDARs on pyramidal cells, normally activated by low-level ambient glutamate, induces activity-independent homeostatic plasticity leading to increased excitatory synaptic inputs onto these neurons and increased gamma oscillations (Miller et al., 2016; Petzi et al., 2023). The disinhibition theory suggests that antagonism or dysfunction of the NMDA receptors on INs decreases the inhibitory tone in the circuit resulting in a higher neuronal activity within the network (Molina et al., 2014; Miller et al., 2016; Johnston

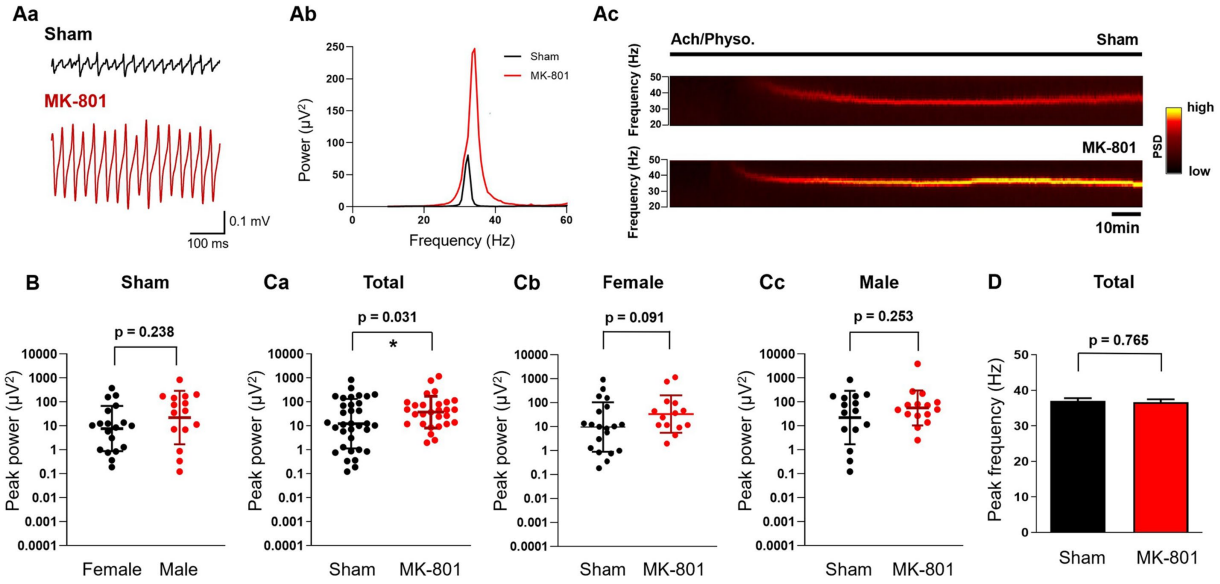

FIGURE 4
Subchronic MK-801 treatment increased the power of *ex vivo* gamma oscillations induced by bath application of ACh and Physo. **(Aa)** Representative local field potential traces in hippocampal CA3 slices of sham and MK-801 treated rats after the application of ACh (10 μM) & Physo (2 μM). **(Ab)** Representative power spectra of cholinergically induced hippocampal gamma oscillations from sham (black) and MK-801 (red) treated animals. **(Ac)** Representative spectrograms from sham (black) and MK-801 (red) treated animals. Horizontal bar indicates the duration of Ach/Physo application. **(B)** Scatter plots of the peak power of cholinergically induced gamma oscillations in female (black) and male (red) sham treated animals. Bars indicate geometric mean and geometric standard deviation factor. **(Ca)** MK-801 (red) increased the peak gamma power compared to sham (black) treated animals. Bars indicate geometric mean and geometric standard deviation factor. **(Cb)** Peak gamma oscillation power in sham (black) and MK-801 (red) treated female rats. Bars indicate geometric mean and geometric standard deviation factor. **(Cc)** Peak power of gamma oscillations in sham (black) and MK-801 (red) treated male rats. Bars indicate geometric mean and geometric standard deviation factor. **(D)** MK-801 did not affect the peak frequency of gamma oscillations. PSD, Power spectral density; $*p < 0.05$.

et al., 2024). This theory assumes that NMDA receptors are either predominantly expressed on cortical INs compared to pyramidal cells (Lisman et al., 2008; Povysheva and Johnson, 2016) or are functionally more conductive, because the most abundant IN type in the cortex, the PV INs, are more depolarized and their receptors are thus less blocked by Mg^{2+} (Grunze et al., 1996; Homayoun and Moghaddam, 2007). This would mean that antagonists might influence this cell type more effectively. Because of their reduced excitability by NMDA receptor antagonism, PV INs require more synchronized inputs resulting in more synchronous perisomatic inhibition and enhanced gamma oscillation power (Spencer, 2009; Jadi et al., 2016).

An important finding of our study is the sex specificity of the MK-801 effect on hippocampal gamma oscillations. Previous studies tested only male animals (Sullivan et al., 2015; Cui et al., 2022) or did not investigate sex effects (Kehrer et al., 2007; Lemercier et al., 2017). Our study is the first that investigated the effect of NMDA receptor antagonists in female and male animals on hippocampal gamma oscillations and shows that MK-801 had a significantly stronger network effect in female rats compared to males. These observations are in accordance with the sex-specific behavioral effects observed in this and previous studies (Hönack and Löscher, 1993; Andiné et al., 1999; Devaud, 2003; Feinstein and Kritzer, 2013). We have two possible explanations for the sex difference. First, the ovarian hormone estrogen in female animals inhibits the expression of cytochrome P450 2D6 (CYP2D6) (Wang et al., 2014; Konstandi et al., 2020), which is the predicted primary metabolizing enzyme of MK-801 (Banerjee et al., 2020). It can be proposed that the applied MK-801 reached higher levels in female animals. Second, estrogen increases the expression of NMDA receptors in the membrane of neurons (Weiland, 1992; El-Bakri et al., 2004; Ikeda et al., 2010) and enhances the NMDA receptor dependent synaptic currents and calcium transients on hippocampal neurons (Foy et al., 1999; Pozzo-Miller et al., 1999). Increased expression of NMDA receptors in the membranes might cause more intense effects of NMDA receptor antagonists as seen in our experiments. A recent study has shown that besides pyramidal cells also PV INs express aromatase (Hernández-Vivanco et al., 2022), the enzyme to produce estradiol (Do Rego et al., 2009). Under these circumstances, NMDA receptor antagonists might have a stronger direct inhibitory or disinhibition effect on the network as discussed above. These considerations might also explain why KA-induced gamma oscillations had a stronger sex-specificity. Since KA receptors seem to preferentially activate interneurons compared to muscarinic ACh receptors (believed to be predominantly expressed on principal cells), KA-induced gamma oscillations are postulated to be generated by a primary stimulation of interneurons (Bartos et al., 2007). The disinhibition theory postulates that interneurons express more functional NMDA receptors, which might be further increased by estrogen in female animals. Thus, NMDA receptor antagonists may disinhibit the interneuron-based KA-induced gamma oscillations in female animals more effectively. Preclinical studies have shown that female animals are more sensitive to treatment with ketamine compared to males and develop more severe side effects (Ponton et al., 2021). These results are not consistent with the existing few human data, where the treatment response after systemic acute low dose ketamine application seems to be similar in women and men (Coyle and Laws, 2015; Freeman et al., 2019; Ponton et al., 2021). The sex

effect of ketamine, however, might depend on the dose applicated because higher (1 mg/kg) dose reduced the Hamilton Depression Rating Scale scores more in women than in men (Freeman et al., 2019). In contrast to the treatment response, the side effects show clear sex-specific differences (Liebe et al., 2017; Ponton et al., 2021) indicating that ketamine acts sex-specifically also in human. Our results suggest that the higher sensitivity in females is not specific to ketamine but seems to be a generic characteristic trait of NMDA receptor antagonists.

In conclusion, presented data demonstrate that longer systemic application of the highly selective, non-competitive, use-dependent NMDA receptor antagonist MK-801 increases the amplitude of hippocampal gamma oscillations. The effects are associated with behavioral alterations such as impaired recognition memory, increased stereotypy and decreased grooming, surrogate symptoms of the cognitive, positive and negative symptoms of schizophrenia, respectively. Both the electrophysiological and behavioral changes were predominantly observed in female animals suggesting a sex-specific effect of NMDA receptor antagonists. The results reproduce electrophysiological and behavioral traits found in patients and in other schizophrenia animal models and suggest that hippocampal gamma oscillations can be used as a biomarker for further research and pharmacological testing.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The animal study was approved by Landesamt für Gesundheit und Soziales, Berlin, Germany. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

TN: Formal analysis, Investigation, Project administration, Visualization, Writing – original draft, Writing – review & editing. ZG: Conceptualization, Formal analysis, Methodology, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Physical exercise for brain plasticity promotion an overview of the underlying oscillatory mechanism

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The global recognition of the importance of physical exercise (PE) for human health has resulted in increased research on its effects on cortical activity. Neural oscillations, which are prominent features of brain activity, serve as crucial indicators for studying the effects of PE on brain function. Existing studies support the idea that PE modifies various types of neural oscillations. While EEG-related literature in exercise science exists, a comprehensive review of the effects of exercise specifically in healthy populations has not yet been conducted. Given the demonstrated influence of exercise on neural plasticity, particularly cortical oscillatory activity, it is imperative to consolidate research on this phenomenon. Therefore, this review aims to summarize numerous PE studies on neuromodulatory mechanisms in the brain over the past decade, covering (1) effects of resistance and aerobic training on brain health via neural oscillations; (2) how mind-body exercise affects human neural activity and cognitive functioning; (3) age-Related effects of PE on brain health and neurodegenerative disease rehabilitation via neural oscillation mechanisms; and (4) conclusion and future direction. In conclusion, the effect of PE on cortical activity is a multifaceted process, and this review seeks to comprehensively examine and summarize existing studies' understanding of how PE regulates neural activity in the brain, providing a more scientific theoretical foundation for the development of personalized PE programs and further research.

KEYWORDS

physical exercise, brain waves, cortical oscillations, plasticity, EEG

1 Introduction

The brain's plasticity refers to its ability to alter its structure and function, which is fundamental for learning, memory, and cognitive processing (Zhao et al., 2020). Physical exercise (PE) enhances neuronal activity and connectivity, thereby promoting brain plasticity through the modulation of neural networks and the facilitation of information transfer (Augusto-Oliveira et al., 2023). PE has emerged as a key modulator of brain plasticity, providing a promising strategy for mitigating cognitive decline and related diseases (Figure 1) (Voss et al., 2013). Neuronal oscillations, defined as rhythmic fluctuations in the electrical potential of groups of neurons, play a crucial role in integrating information within a common network (Rosenblum et al., 2022). These oscillations are essential drivers of interaction, communication, and information transfer in the brain and may be associated with certain mental disorders (Han, 2023; Wang et al., 2024). Non-invasive imaging techniques are significant methodologies for monitoring neural oscillations,

with electroencephalography (EEG) being a commonly used tool in this field (Hosang et al., 2022). Various EEG frequency bands (delta, theta, alpha, beta, and gamma) are generated by distinct neuronal populations in different brain regions (Han et al., 2021a,b). Understanding the role of oscillations in neuronal function regulation is crucial for deciphering the effects of PE on the brain (Wang et al., 2023). Measuring neural oscillations before and after exercise can elucidate how physical activity influences cognitive function.

Physical activity (PA) encompasses any bodily movement that results in energy expenditure (EE) through skeletal muscle contraction. Physical exercise (PE), a key element of PA, is characterized by planned, structured, and repetitive physical movements aimed at improving or maintaining various components of physical fitness (Caspersen et al., 1985; Murphy et al., 2016). It includes activities such as brisk walking, running, swimming, cycling, ball games, dancing, and weight lifting (Qiu et al., 2023). Both PA and PE enhance cognitive performance by stimulating molecular mechanisms such as brain-derived neurotrophic factor (BDNF) (Vedovelli et al., 2017), learning (Guo et al., 2020), and memory (Wheeler et al., 2020). Interventions focused on increasing planned and organized activities often use the term "physical exercise" instead of "physical activity" (Gallardo-Gómez et al., 2022). To improve health, the American College of Sports Medicine recommends engaging in aerobic and resistance exercises on a regular weekly basis (Weiss et al., 2023). Studies find that PE significantly influences spatial memory, working memory, and executive attention (Chaire et al., 2020). Aerobic exercise enhances spatial memory by promoting hippocampal neurogenesis and increasing BDNF levels (El-Sayes et al., 2019; Stern et al., 2019). Resistance exercise, on the other hand, strengthens executive function by increasing prefrontal cortex volume and thickness (Chow et al., 2021). Research indicates that exercise intensity plays a crucial role in cognitive benefits, with high-intensity exercise potentially offering greater advantages than low-intensity exercise (Stern et al., 2019).

Moreover, various forms of mind-body exercises, such as yoga, Tai Chi, and dance, have gained popularity in recent years. Mind-body exercise employs a mind-body approach to achieve both physical and mental benefits through physical activity (Chan et al., 2017). Additionally, specific interventions like Positive Thinking Yoga have been shown to positively impact the mental wellbeing of individuals with Parkinson's disease (Kwok et al., 2019). Ultimately, the effectiveness of exercise in preventing or treating diseases is influenced by factors such as the type, duration, frequency, and intensity of the exercise (Guo et al., 2020; Qiu et al., 2023).

Thus, this review explores the possible neural mechanisms by which PA influences brain and cognitive functions by examining and synthesizing the relevant literature to date from four perspectives: (1) effects of resistance and aerobic training on brain health via neural oscillations; (2) how mind-body exercise affects human neural activity and cognitive functioning; (3) age-Related effects of PE on brain health and neurodegenerative disease rehabilitation via neural oscillation mechanisms; and (4) conclusion and future direction.

2 Effects of resistance and aerobic training on brain health via neural oscillations

Regular exercise at moderate intensity, encompassing activities such as strength training, endurance exercises, balance routines, flexibility exercises, and coordination drills, positively contributes to all aspects of human health (Qiu et al., 2023). However, sudden high-intensity workouts in untrained individuals can trigger adverse cardiovascular events (López-Otín and Kroemer, 2021). Hence, the intensity and nature of training play pivotal roles in producing beneficial health outcomes (Qiu et al., 2023). The protective impact of both short-term and long-term exercise on the central nervous system against neurodegeneration and cerebrovascular diseases has garnered significant interest from researchers (Liu et al., 2019; Qiu et al., 2023). Neuroplasticity is central to this Vints et al. (2022). Neuroplasticity, the brain's ability to undergo functional and structural changes in response to internal or external stimuli, plays a crucial role in this context (Voss et al., 2017b).

Neuroplasticity is closely linked to neural oscillations, which interact and play a key role in brain function and adaptability (Tavano et al., 2023; Weiss et al., 2023). Oscillations are pivotal in regulating physiological processes during exercise, conscious perception, and cognitive functions (Van Ede et al., 2018). These oscillations are categorized into frequency bands, including delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (30–100 Hz) waves (Steriade et al., 1990). By examining these neuronal rhythms, correlations between alterations in cognitive function and brain health can be established, offering insights into the effects of these oscillations on overall brain functioning (Figure 2). Despite conclusive evidence supporting the neuroprotective effects of exercise, whether each specific type of exercise entails distinct neuroprotective mechanisms remains debated in the realm of sports medicine (Ciria et al., 2018). Moreover, the comparative effectiveness of various exercise modalities remains contentious and requires further investigation (Liu et al., 2019).

Resistance training, defined as any physical activity involving the generation of muscular force against external resistance to enhance muscle size, strength, and endurance, is a fundamental component of physical fitness (Chow et al., 2021). Studies have established a correlation between low skeletal muscle mass or impaired muscle function and cognitive dysfunction (Oudbier et al., 2022; Peng et al., 2023). Neurological adaptations to resistance training, particularly observed within the first 6–8 weeks of initiating a regimen, often result in rapid strength gains even in the absence of muscle hypertrophy (Folland and Williams, 2007). Resistance exercise (RE) can activate various neurochemicals, including lactate, cortisol (COR), BDNF, norepinephrine, and dopamine (Hsieh et al., 2016). Harveson et al. (2016) reported the beneficial impact of acute moderate resistance exercise (70% 1RM) on working memory in male adults aged 21–30 and older adults aged 65-72. However, these health benefits of acute resistance exercise may be short-lived. Following acute isometric RE in the lower extremities, Basso and Suzuki (2017) observed a temporary elevation in peripheral

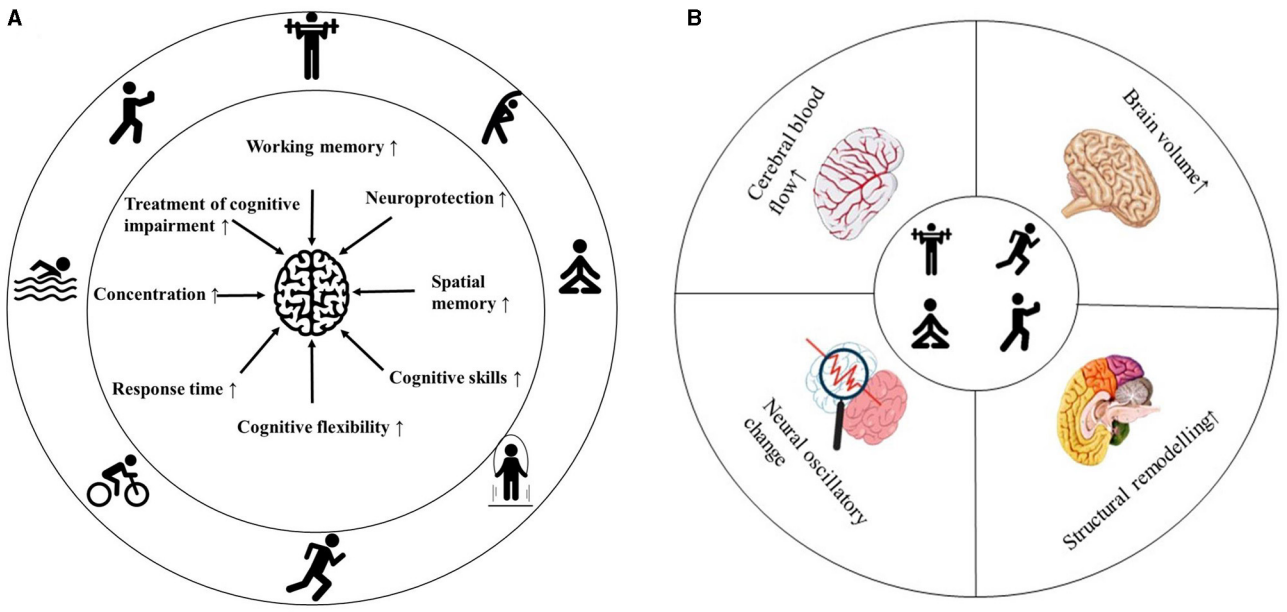

FIGURE 1
Summary of the effects of exercise on brain health. Effects of exercise on cognitive behavior **(A)**. Exercise-induced changes in brain physiology **(B)**.

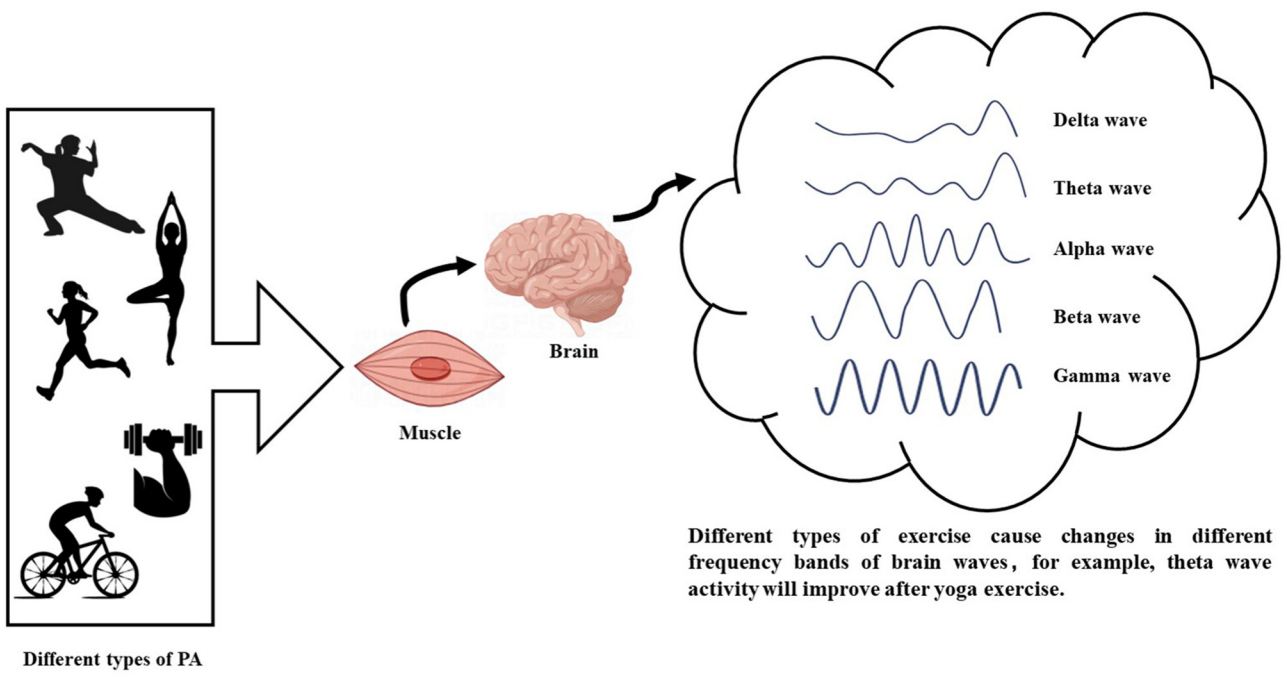

FIGURE 2
Different types of exercise affect different bands of brain waves.

blood levels of IGF-1, with cognitive benefits lasting up to 2 h post-exercise. Conversely, older adults engaged in 52 weeks of resistance exercise displayed increased peripheral blood IGF-1 levels and enhanced cognitive performance (Tsai et al., 2019). Moreover, skeletal muscles are known to secrete neurotrophic and muscle factors such as insulin-like growth factor-1 and BDNF, fostering structural and functional plasticity in brain regions like the hippocampus and prefrontal cortex (Broadhouse et al., 2020; Coutinho et al., 2022). This release of growth factors, not exclusive to resistance exercise, may be a key mechanism (Nicola et al., 2024). Long-term neural structure and function are likely supported by resistance exercise through this mechanism, potentially enhancing cognitive function through improved skills and muscle-related adaptations.

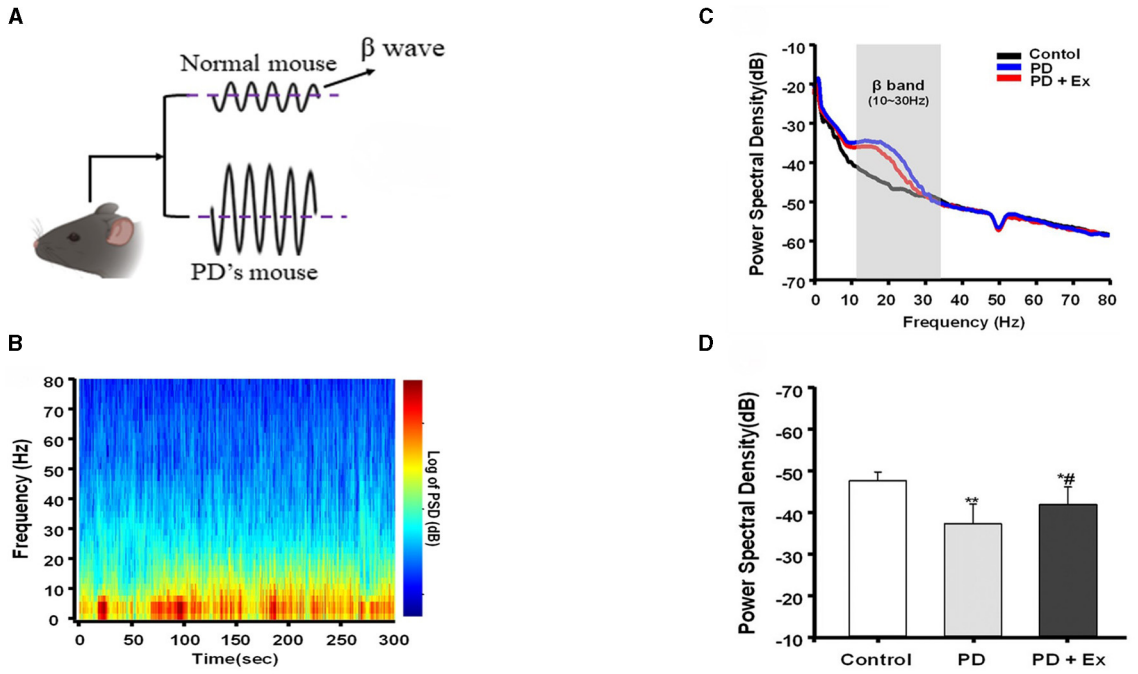

FIGURE 3
Beta burst dynamics in PD. Increased β pulse amplitude appears in PD mouse model **(A)**. β bursts mitigated by exercise intervention (Yu et al., 2021). **(B–D)** Are replotted based on Liu (2021). A representative fast Fourier transform (FFT)-based spectrogram depicts the time-frequency spectral power of motor cortex LFPs during 5-min epochs of rest **(B)**. Linear graphs show averaged LFP power (0–80 Hz) spectra for the Control, Parkinson's disease (PD), and PD + exercise (Ex) groups **(C)**, with the gray area showing that the beta band in the 10–30 Hz range of LFP power was significantly increased in 6-hydroxydopamine (6-OHDA)-lesioned rats. The average PSDs of the three groups are shown in **(D)**. $^{*}P < 0.05$, $^{**}P < 0.01$; and compared with the PD group, $^{\#}P < 0.05$.

In recent years, researchers have endeavored to elucidate the relationship between resistance training and neural oscillations, aiming to provide a more comprehensive understanding of the effects of resistance exercise on brain function from alternative perspectives (Weiss et al., 2023). A study showed that a physical activity program for 4 months led to an increase in frontal alpha activity during an attention task, suggesting an improvement in the neural dynamics linked to visual attention (Chaire et al., 2020). Furthermore, studies have been conducted to determine how different exercise regimens affect muscle strength and cognitive performance. These studies demonstrate that brief, intense resistance training can positively affect neural oscillations and brain plasticity, resulting in improved cognitive performance and synaptic plasticity (Harrison et al., 2019; Nuzzo et al., 2024). In a separate investigation into the impact of resistance exercise therapy on individuals with mild cognitive impairment, a notable decline in theta band power was documented following 12 weeks of group resistance training (Chmielewski et al., 2021). While resistance training is increasingly used in clinical settings, more research is needed to determine the most effective dosage for optimal health effects.

In addition to resistance training, aerobic exercise represents another common form of PE. Comparative analyses of systematic reviews and meta-analyses from the past 5 years suggest that aerobic exercises such as walking, jogging, and cycling are more frequently employed in research aimed at improving cognitive health compared to resistance training (Lesinski et al., 2015; Sáez de Asteasu et al., 2017; Northey et al., 2018; Gavelin et al., 2021; Kwok et al., 2022). This preference may stem, in part, from the accessibility and simplicity of aerobic exercises. Aerobic activities are straightforward to perform, often requiring minimal specialized equipment and supervision, making them suitable for incorporation into daily routines, particularly for untrained individuals and those with cognitive impairments (Chow et al., 2021). Results from numerous studies involving humans and animals suggest that voluntary running in rodents or aerobic training in humans can enhance brain plasticity, including synaptogenesis, neurogenesis, and cognition (Falkai et al., 2017). Several meta-analyses focusing on adults aged over 55 have highlighted the beneficial effects of aerobic exercise on attention, processing speed, executive function, memory, and working memory (Falkai et al., 2017; Northey et al., 2018). Additionally, a study by Stern et al. found that 6 months of aerobic exercise positively impacted brain health in healthy individuals aged 20 to 67 years. A study on neural oscillations revealed that participants in the exercise group experienced an increase in frontal alpha power magnitude after a 4-month aerobic exercise program, as measured using the Visual Attention Search Task (VAS) (Chaire et al., 2020). In a study investigating the neural mechanisms of aerobic exercise-induced hyperalgesia, participants exhibited reduced pain scores in the tibialis anterior and rectus femoris muscles following moderate-intensity aerobic exercise, accompanied by increased power of alpha oscillations, indicative of central descending inhibition (Zheng et al., 2021). Decreases in task-related power within the beta

band of sensorimotor regions, as measured by EEG, are believed to indicate heightened cortical activation and active processing of motor tasks (Gerloff et al., 1998; Engel and Fries, 2010). The alpha and beta bands experienced an increase in EEG coherence after a single session of aerobic exercise, with the highest level of improvement observed in the high beta band (Mark et al., 2023). The following are potential underlying mechanisms that can improve cognitive function through aerobic exercise.

Aerobic exercise has become the cornerstone of clinical management for various neurodegenerative diseases. However, the intensity of aerobic exercise has been a subject of controversy in research (Tsai et al., 2019; Sudo et al., 2022). In a study analyzing the effects of a single 25-min moderate-intensity exercise intervention in older adults, the experimental group exhibited improved motor performance on the force modulation task immediately post-exercise compared to the control group (Hübner et al., 2018). However, many studies indicate that high-intensity aerobic exercise [≥80% of maximal power output, ≥80% of maximal oxygen uptake (VO2)] may lead to brain and cognitive damage (Komiyama et al., 2020; Stone et al., 2020). Recently, a narrative review emphasized the impact of aerobic exercise on cerebral blood flow (CBF), cerebral oxygenation, and cerebral metabolism (Sudo et al., 2022). It was noted that there is a gradual increase in CBF during light to moderate-intensity exercise, whereas high-intensity exercise leads to a decrease in CBF. This suggests that the metabolic demands of the brain may not be met during high-intensity exercise, potentially negatively impacting cognition and brain health.

Even though overwhelming evidence suggests that physical exercise improves brain health and cognitive function, concerns remain. Sports-related concussions (SRCs) are frequently experienced by athletes due to biomechanical forces to the head, resulting in transient clinical signs, symptoms, and dysfunction (Chmielewski et al., 2021). EEG is often utilized clinically for diagnosing moderate to severe traumatic brain injury (TBI), monitoring acute and subacute neurophysiological changes, and serving as a prognostic indicator for the patient's clinical presentation and recovery (Corbin-Berrigan et al., 2023). It is increasingly recognized that excessive exercise could result in brain damage. While EEG is not the primary method for monitoring and treating sudden cardiac death (SCD) in clinical settings, it proves valuable for detecting potential abnormalities (Rapp et al., 2015; Kamins et al., 2017). EEG abnormalities have been identified in patients with SRC in some studies. Research conducted by Teel et al. (2014) revealed that concussed participants exhibited reduced alpha, beta, and theta bandwidths, particularly showing a significant reduction in beta power during computerized neurocognitive testing (ImPACT). In a study that gathered EEGs from concussed patients, analysis revealed alterations in the alpha and beta frequency bands that significantly correlated with Glasgow Coma Scale (GCS) scores (Frohlich et al., 2022). Specifically, higher GCS scores were associated with reduced alpha power and increased beta power. These findings highlight the importance of monitoring and analyzing oscillations in different frequency bands following injury for accurate diagnosis and prognosis in post-injury care (Frohlich et al., 2022). Caution should be exercised regarding excessive physical activity due to its potential adverse impact on brain health.

In recent years, researchers have shown increased interest in various forms of exercise due to the differing needs of diverse populations. Mind-body exercises such as yoga, Tai Chi, and dance have been utilized in the treatment of some chronic diseases. Further research on the effects of these types of exercises on brain health is necessary.

3 How mind-body exercise affects human neural activity and cognitive functioning

Recent studies have focused on the potential benefits of mind-body exercises, such as yoga, dance, and Tai Chi, on brain health (Gothe et al., 2019). Mind-body exercise, a form of physical exercise that utilizes a mind-body approach to achieve physical and mental benefits, has garnered significant attention from researchers (Kwok et al., 2019). Despite its lower intensity compared to other forms of exercise, mind-body exercise still offers specific health benefits that have piqued researchers' interest.

Dance is a multifaceted activity that includes physical exercise and cognitive, social, and artistic components, which are linked to visual-spatial, cognitive, and executive functions in individuals (Chirles et al., 2017; Karkou et al., 2019). It has been demonstrated that dance can enhance cognitive and executive functioning, especially in individuals with mild cognitive impairment (Qi et al., 2019; Zhu et al., 2020). A recent systematic review further supports the idea that dancing can lead to increased cognitive stimulation, promoting neuroplasticity in the brain (Teixeira-Machado et al., 2019). Dance interventions have been shown to positively impact brain plasticity, causing various structural changes, such as increases in gray matter volume and white matter integrity (Teixeira-Machado et al., 2019). An experiment was conducted by Qi et al. (2019) utilizing functional magnetic resonance imaging (fMRI) assessed changes in brain activity using the amplitude of low-frequency fluctuations (ALFF) metric. The results revealed that older adults with mild cognitive impairment who participated in the dance intervention group exhibited increased ALFF in brain regions, including the bilateral frontotemporal, insular, anterior cingulate, and parahippocampal cortex. Additionally, substantial cortical thickening was observed in specific regions of the right hemisphere in the dance intervention group (Rektorova et al., 2020). The positive impacts of dance interventions on brain structure and function suggest that improvements in cognitive functioning may be achievable through dance therapy (Wu et al., 2021). Notably, a study reported a significant increase in white matter volume in frontal and parietal regions, as well as in the corpus callosum, following a 6-month dance intervention (Voss et al., 2017a; Rektorova et al., 2020). The engagement of cognitive, somatosensory, and motor regions in complex dance movements can have subtle yet beneficial effects on cognitive functions (Wu et al., 2021). Dance therapy has also been credited with enhancing coordination between neurosensory and muscular systems, increasing flexibility, and muscular strength in both the upper and lower extremities (Douka et al., 2019; Chan et al., 2021). While existing studies have confirmed the positive health effects of dance interventions on both the brain and body, further research

with larger sample sizes and extended interventions is warranted. This is due to the necessity of comprehensive instruction and coaching in dance, as well as the ongoing need to explore the underlying physiological mechanisms more extensively.

Yoga, considered a common mind-body exercise intervention alongside dancing, is a positive movement practice that allows individuals to move gradually and safely into physical postures while emphasizing relaxation, full breathing, and awareness of physical sensations and thoughts (Gothe et al., 2019). One study revealed that experienced yoga practitioners exhibited greater overall brain gray matter volume (GMV) compared to non-practitioners (Villemure et al., 2015). In a study conducted over 3 months by Krause-Sorio et al. (2022) older women at risk for Alzheimer's disease who engaged in weekly yoga training and completed assignments punctually demonstrated retention of GMV across all brain regions, as well as increased volumes in the left precentral cortex and lateral occipital cortex. Several studies have examined the effectiveness of combining transcranial direct current stimulation (tDCS) with yoga interventions. These studies have shown that the combination of yoga and active tDCS leads to improved subnetwork connectivity across all EEG frequency bands (Sefat et al., 2022). These results hint at the possible physiological mechanisms underlying yoga's cognitive benefits. Recent recognition of yoga as a safe practice with positive cognitive effects in healthy older adults, those with mild cognitive impairment (MCI), and early-stage dementia patients is noteworthy (Brenes et al., 2019; Chobe et al., 2020). A randomized controlled trial revealed that yoga had a moderately significant impact on cognition, with attention and processing speed, executive function, and memory ranking as the top three affected domains (Voss et al., 2023). Although comparing the effects of various yoga interventions remains challenging due to the diversity in Hatha Yoga styles, these discrepancies could open new avenues for future research as they may lead to varying impacts on the nervous system (Voss et al., 2023). The growing recognition of yoga as an effective exercise intervention, along with ongoing exploration of its therapeutic effects on neurological disorders, points to the potential for optimized outcomes when combined with clinical treatments.

In recent years, the growing popularity of Tai Chi Chuan (TCC) as a physical and mental exercise can be attributed to its multifaceted health benefits (Wayne et al., 2014). Originating in China during the 17th century AD (Yang et al., 2022). TCC has been linked to positive changes in brain function and structure in various studies. For instance, a study involving a 40-week TCC intervention revealed a significant increase in brain volume (Yang et al., 2022). Furthermore, a functional magnetic resonance imaging (fMRI) study showed that a 12-week TCC intervention led to improvements in subjects' low-frequency fluctuation (fALFF) scores in the lateral prefrontal cortex compared to a control intervention (Yue et al., 2020). Such enhancements in specific brain regions can potentially alleviate age-related memory loss. Notably, older women with 6 years of Tai Chi experience demonstrated greater homogeneous activation of spontaneous regions in temporal areas, including the fusiform gyrus and hippocampus, compared to those engaging in 6 years of walking as a control intervention, as indicated by another fMRI study (Yue et al., 2020). Moreover, systematic evaluations and meta-analyses have underscored the positive impact of TCC on overall cognitive functioning, memory, learning, and visual perception among patients with cognitive impairment (Yang et al., 2020). However, experimental studies have failed to establish the superiority of TCC over control interventions in improving depressive symptoms or executive function (Wei et al., 2022). There is a lack of conclusive evidence supporting the notion that Tai Chi is more effective in addressing these features than alternative control methods. This underscores the need for further research to elucidate the precise benefits of TCC on physical and mental health, along with the underlying neural mechanisms supporting these effects.

With increasing interest in mind-body exercises such as yoga and Tai Chi, which offer the flexibility to adjust exercise loads and cater to a wider range of individuals, including the elderly and those with neurological conditions, it is evident that these exercises are becoming more popular. The debate surrounding adaptive movement patterns persists due to the insufficient availability of reliable monitoring instruments (Chaire et al., 2020). Therefore, it is crucial to conduct further research to elucidate the underlying neural mechanisms, necessitating a better understanding of their impact (Yang et al., 2020; Wei et al., 2022).

4 Age-related effects of PE on brain health and neurodegenerative disease rehabilitation via neural oscillation mechanisms

The advent of neuroimaging technology has enabled the non-invasive monitoring of human brain activity. However, these methods have inherent limitations that hinder the exploration of intricate neural mechanisms. Factors such as low amplitude, artifacts, and resistance to wearing electrode caps can adversely affect the accuracy of EEG signals (Baumgartner and Koren, 2018). Additionally, age (Borhani et al., 2021), health conditions (Weiss et al., 2023), and other factors can impact brain health and function. The role of neural oscillations and PE in brain health requires further research.

Changes in structural brain functioning linked to age-related cognitive decline, also known as normal cognitive aging, have been well-documented (Jafari et al., 2020). Individuals undergoing physiological aging often demonstrate increased power of low-frequency oscillations and a decrease and slowing of alpha activity, as observed in resting-state EEG (rsEEG) studies (Nobukawa et al., 2019). Consistent findings have shown shifts in oscillatory activity from posterior to anterior regions in older adults, characterized by an increase in frontal activity and a decrease in occipital activity (Perinelli et al., 2022). Specifically, the power spectral density (PSD) tends to plateau at 2–24 Hz in older adults compared to their younger counterparts, indicating alterations in brain activity with age (Voytek et al., 2015). Research has revealed that both slow and fast gamma power decrease with age, with a more pronounced decrease observed in fast gamma power (Murty et al., 2020). This decline in gamma power was further corroborated by another study, which showed age-related reductions in gamma power in the motor region, suggesting the generalizability of this phenomenon across various brain regions (Gaetz et al., 2020). Given the

known involvement of the gamma band in higher cognitive functions such as attention and working memory, the observed changes in gamma band activity in older adults align with the hypothesis that cognitive decline is associated with aging (Murty et al., 2020). Moreover, a substantial relationship between memory retrieval accuracy and rsEEG band power has been established. Increases in alpha and beta bands in the right parietal and right frontal lobes have been found to be significantly associated with decreased memory retrieval accuracy (Borhani et al., 2021). These findings underscore the importance of understanding the neural mechanisms underlying age-related cognitive changes and highlight the potential utility of rsEEG measures in predicting cognitive performance in older adults.

The risk of developing neurodegenerative diseases like Parkinson's disease (PD) and Alzheimer's disease (AD) increases with age (Mattson and Arumugam, 2018). PD is a prevalent neurodegenerative disorder clinically characterized as a "movement disorder" due to symptoms such as stiffness and bradykinesia. Excessive activity in the beta band is a hallmark of basal ganglia signaling in PD patients, characterized by sudden bursts rather than continuous elevation. Prior studies have elucidated that prolonged beta bursts in PD contribute to heightened oscillatory synchronization within the subthalamic nucleus (STN), impeding the encoding capacity of local circuits (Tinkhauser et al., 2018). Consequently, researchers have probed whether animal models of PD exhibit similar alterations in beta activity within the basal ganglia following dopamine loss and resultant motor dysfunction. This exploration has facilitated direct comparisons of synchronized activity across various behaviors between control and dopamine-deprived groups (Avila et al., 2010), illuminating the origins and ramifications of synchronous increases in basal ganglia output within the beta range (Figure 3). One study discovered that bilateral electrodes implanted in the substantia nigra pars reticulata (SNpr) of rats with unilateral damage revealed a correlation between dopamine loss and heightened spike activity in both local field potential (LFP) power and beta frequency ranges (Johansson et al., 2022).

The surge in activity was predominantly observed in the high-frequency range while the rats walked on a circular treadmill, with the most pronounced activity occurring in the low-frequency range during periods of inattentive rest (Avila et al., 2010). Although the experimental design of the rodent study could not precisely determine the timing of muscle activity following reawakening from a state of inattentive rest, it facilitated a direct comparison between the damaged and undamaged hemispheres during complex and sustained exercise (Avila et al., 2010). The study indicated that the loss of dopamine significantly impacted the synchronization of output from the basal ganglia beta region in rats walking on a treadmill. Studies conducted on semi-Parkinsonian rats have demonstrated that dopamine depletion is linked to increased expression of low-frequency activities during rest, which diminishes with exercise (Palasz et al., 2019). These results suggest that abnormal beta wave activity is associated with impaired motor function and that exercise interventions in laboratory animals can modulate beta wave activity (Tinkhauser et al., 2018; Palasz et al., 2019). This presents a novel avenue for the treatment and monitoring of patients with Parkinson's disease.

AD is another common degenerative disease that, like Parkinson's disease (PD), becomes more prevalent with age. Gamma oscillations, which are rhythmic fluctuations of local field potentials (LFPs) with a frequency range of approximately 25–100 Hz, are a notable feature in various brain regions, such as the hippocampus (Mably and Colgin, 2018). These oscillations are believed to be involved in attention selection and memory processes (Bieri et al., 2014). Studies have shown that the amplitude of slow gamma oscillations tends to increase during the proper execution of tasks involving associative memory, particularly when cue-induced memory retrieval is anticipated. As a result, researchers hypothesize that certain cognitive disorders associated with brain diseases may be linked to disturbances in gamma rhythms (Bieri et al., 2014; Mehak et al., 2022).

Findings from a study revealed that 3xTg mice exhibited a decrease in the slow gamma power of the hippocampus CA1 within a familiar circular orbit, alongside an unstable spatial representation of CA1 place cells, and a reduction in the slow gamma coordination of CA1 place cells' discharge (Mably et al., 2017). This slow gamma impairment could potentially lead to the incomplete retrieval of stored spatial information from CA3 to CA1. These results suggest that targeting slow gamma interference could offer a promising new avenue for addressing memory deficits in Alzheimer's disease (Booth et al., 2016). It has been demonstrated that exercise enhances neurotrophic factors, growth factors, and synaptic markers, and reduces neuroinflammation, making it a key strategy for both the prevention and treatment of Alzheimer's disease, often in conjunction with medications (Cotman et al., 2007; Cho et al., 2015). In a study combining 40 Hz light stimulation with exercise in the 3xTg mouse model, significant improvements were observed after a 12-week intervention period (Park et al., 2020). These included a reduction in tau phosphorylation and Aβ levels in the hippocampus, as well as enhancements in spatial learning, memory, long-term memory, mitochondrial function, and neuroplasticity. Although this study did not directly measure gamma oscillations, previous research has shown that alterations in hippocampal gamma oscillations occur over time and with Aβ levels (Kurudenkandy et al., 2014), with the 3xTg-AD model displaying abnormal synchronization of beta and gamma frequencies (Castano-Prat et al., 2019).

The lack of clinically recognized medications or medical treatments for degenerative diseases has propelled exercise to the forefront as a key intervention method (De la Rosa et al., 2020). Long-term exercise training has beneficial effects on delaying physiological memory loss, making it an effective strategy for preventing age-related memory loss and neurodegeneration (De la Rosa et al., 2020). One study demonstrated that 6 months of exercise (60 min per session, 3 days per week) increased gray and white matter in the anterior cingulate cortex in cognitively healthy older adults, as measured by magnetic resonance imaging (Sebastián-Romagosa et al., 2020). Through the analysis of EEG signals, exercise-induced changes can be objectively assessed, enabling the examination of physiological transformations in the brain (Albert et al., 2011). Mild cognitive impairment (MCI) represents a transitional phase between normal aging and early dementia, characterized by a decline in certain cognitive functions (Albert et al., 2011). Clinical research has shown that prolonged

exercise training over a period of 6 to 12 weeks can lead to a reduction in delta and theta band power, along with an elevation in beta and alpha band power, as well as increased EEG complexity and connectivity in patients with MCI (Pedroso et al., 2021). These findings suggest that cortical activity and cognition in individuals with MCI may be improved by exercise, as evidenced by these observed alterations.

Animal model experiments also showed the benefits of PE. In a transgenic mouse model of AD, voluntary and forced exercise interventions led to a decrease in amyloid-beta (Aβ) plaques and neurofibrillary tangles (NFTs). Improvements in learning and memory were correlated with these findings in some cases (Ohia-Nwoko et al., 2014; Tapia-Rojas et al., 2015). A recent study found that treadmill exercise for 12 weeks as part of an AD intervention program increased mitochondrial proteostasis in mice. Concurrently, the exercised mice exhibited a marked decrease in escape latency and a significant increase in crossings over the platforms in the water maze test (Cui et al., 2023). Research has shown that 4 weeks of sustained platform-running exercise can positively impact the plasticity of motor cortex function in rats with PD (Liu, 2021). Specifically, this exercise regimen led to the amelioration of abnormal neural activity in the primary motor cortex (M1) region of PD rats. The disruption of M1 neurons and beta oscillations due to the exercise intervention was evidenced by changes in oscillatory patterns (Liu, 2021). A notable finding was the decrease in spiking phase locking of beta band oscillations observed in the motor intervention group compared to the PD group. Additionally, voluntary running exercise has been found to enhance BDNF expression in the dorsal striatum of PD model mice (Bastioli et al., 2022). This study also found a notable increase in extracellular dopamine concentrations in the striatum of the exercise group. The importance of dopamine (DA) in exercise, motor learning, reward, motivation, and emotion cannot be overstated (Schultz et al., 2017; Athalye et al., 2018). Exercise has the potential to alleviate motor deficits in PD by slowing down the neurodegeneration of DA neurons (Bastioli et al., 2022). These studies suggest that exercise plays a pivotal role in the prevention and treatment of neurodegenerative diseases, demonstrating positive effects on behavior and brain plasticity in both animal and clinical trials (Cotman et al., 2007; Avila et al., 2010; Kurudenkandy et al., 2014; Tinkhauser et al., 2018; Park et al., 2020; Lee et al., 2021).

As individuals age, their brains undergo several changes that can lead to cognitive decline and slowed responses (Borhani et al., 2021). These changes, although subtle, can have a lasting and significant impact on an older person's life (Machado et al., 2019). Despite the absence of pharmaceutical agents specifically recommended for treating and preventing this degenerative process, exercise emerges as a potentially effective and accessible alternative. Monitoring changes in the brain's oscillations allows for timely adjustments to the exercise program (Wan et al., 2024). While numerous studies have highlighted the benefits of exercise on brain health and cognitive functioning, some have reported a weak association between exercise and cognitive performance (Iso-Markku et al., 2024). To achieve superior intervention outcomes, it is imperative to identify more effective methods to supplement single exercise interventions.

5 Conclusion and future direction

As previously highlighted, abundant evidence supports the significant impact of exercise on brain health, including enhancements in cognitive abilities, alterations in neuronal oscillatory activity, and other mechanisms across the lifespan in both healthy and pathological conditions. However, variations in task paradigms, age, gender, intervention duration, exercise type, and other protocols introduce considerable heterogeneity among studies, sometimes leading to conflicting results regarding the exercise-brain relationship (Browne et al., 2017; Vanderbeken and Kerckhofs, 2017; Gallardo-Gómez et al., 2022). For instance, a recent systematic review and meta-analysis in humans concluded that there may not be a linear association between exercise and cognition, particularly among older adults (Gallardo-Gómez et al., 2022). This study also revealed differential dose-response relationships for various exercise modalities, with resistance training potentially offering superior efficacy compared to other forms (Gallardo-Gómez et al., 2022). Against this backdrop, the standardization of research methodologies in this field is paramount (Augusto-Oliveira et al., 2023). This entails the harmonization of exercise protocols, including modality, design, intensity, and duration, as well as consideration of the timing of interventions relative to injury or neurodegenerative disease diagnosis and the characteristics of the study population. Essential aspects to be addressed include interference controls, cognitive function assessment methodologies, monitoring techniques, and the timing of outcome evaluations. Moreover, increasing sample sizes, particularly in human studies, is imperative due to the substantial heterogeneity among individuals, necessitating larger cohorts for robust conclusions and result replication (Augusto-Oliveira et al., 2023).

Combinations of different exercise modalities have garnered attention in research due to their reported effects on brain health and neural oscillations (Gothe et al., 2019; Yang et al., 2020). Identifying specific subgroups of individuals who stand to benefit most from particular physical activities is essential for tailoring personalized exercise regimens based on individual or group characteristics. Evolving data acquisition technology now allows for the simultaneous acquisition of EEG and EMG signals, enhancing the feasibility of research. This simultaneous capture during exercise enhances researchers' understanding of the muscle-brain relationship and facilitates the exploration of the deeper connections between physical activity and neural processes. Known as corticomuscular coherence (CMC), the coupling of sensorimotor cortical rhythms and muscle activity serves as a fundamental aspect of this investigation (Bourguignon et al., 2019). Through the analysis of EEG and EMG signals during movement, researchers can delve into the intricate relationship between the brain and physical motion.

In summary, physical activity is a crucial approach to preserving health and combating cognitive decline and neurodegenerative disorders. The importance of these variables when developing a personalized exercise prescription is due to the potential for disparate health effects based on the specific type and intensity of exercise. During exercise, neural oscillation changes provide new insights into monitoring the therapeutic effectiveness of PE and making prompt adjustments to the exercise

program. Future studies may employ simultaneous brain and electromyography acquisition to further probe the nuanced interplay between exercise and brain functions. This knowledge holds considerable potential for advancing the development of precise non-pharmacological interventions aimed at enhancing brain health, preventing related diseases, and informing the creation of evidence-based personalized exercise prescriptions.

Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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The neuromechanical of Beta-band corticomuscular coupling within the human motor system

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Beta-band activity in the sensorimotor cortex is considered a potential biomarker for evaluating motor functions. The intricate connection between the brain and muscle (corticomuscular coherence), especially in beta band, was found to be modulated by multiple motor demands. This coherence also showed abnormality in motion-related disorders. However, although there has been a substantial accumulation of experimental evidence, the neural mechanisms underlie corticomuscular coupling in beta band are not yet fully clear, and some are still a matter of controversy. In this review, we summarized the findings on the impact of Beta-band corticomuscular coherence to multiple conditions (sports, exercise training, injury recovery, human functional restoration, neurodegenerative diseases, age-related changes, cognitive functions, pain and fatigue, and clinical applications), and pointed out several future directions for the scientific questions currently unsolved. In conclusion, an in-depth study of Beta-band corticomuscular coupling not only elucidates the neural mechanisms of motor control but also offers new insights and methodologies for the diagnosis and treatment of motor rehabilitation and related disorders. Understanding these mechanisms can lead to personalized neuromodulation strategies and real-time neurofeedback systems, optimizing interventions based on individual neurophysiological profiles. This personalized approach has the potential to significantly improve therapeutic outcomes and athletic performance by addressing the unique needs of each individual.

KEYWORDS

beta oscillation, brain-muscle, corticomuscular coupling, motor system, training status

1 Introduction

Beta-band corticomuscular coherence (Beta-CMC) is a crucial aspect of sensorimotor integration, reflecting the interaction between the brain and muscles during movement. This introduction provides a focused overview of Beta-CMC, emphasizing its significance and relevance to motor control and sensorimotor functions.

Neural oscillations, particularly within the Beta-frequency band (12–30 Hz), are prominent in sensorimotor-related cortical and subcortical regions (Whittington et al., 2000; Kilavik et al., 2013). These oscillations are key features of neural activity and can be measured non-invasively in humans (Sherman et al., 2016; Wang et al., 2023). Beta-CMC, the coherence of Beta-band activity between the brain and muscles, is observed during isometric output and varies with the regulation of force and task precision (Koelewijn et al., 2008; Davis et al., 2012; Heinrichs-Graham et al., 2017). Beta-CMC is integral to motor planning,

execution, and regulation (Kristeva et al., 2007; Mehrkanoon et al., 2014). It is modulated by peripheral inputs, highlighting the complex relationship between the brain and muscles (Riddle and Baker, 2005; Witham et al., 2011; Budini et al., 2014; Mehrkanoon et al., 2014). Understanding Beta-CMC provides insights into motor skill learning, control, and functional recovery in motor system disorders (Choi et al., 2020).

Understanding the interplay between neural oscillations and sensorimotor systems is pivotal for deciphering human motor control and its dysfunctions. Variations in research paradigms have so far obscured the clear delineation of this relationship, with the complexity of interactions between the cerebral cortex and motor systems still largely elusive (Khanna and Carmena, 2017).

This review aims to summarize findings on the dynamics of Beta-band oscillations and Beta-CMC in the sensorimotor system, focusing on their role in corticomuscular coupling and modulation during different motor phases and conditions. By integrating multisensory information, this review seeks to understand Beta-oscillations in motor control under both normal and pathological states. It will discuss recent research on pharmacological approaches and advanced brain stimulation techniques to uncover the mechanisms of Beta-band activity during sensorimotor tasks (Barone and Rossiter, 2021). The outcomes of this review aim to enhance our understanding of sensorimotor dysfunctions, leading to more precise and effective therapeutic interventions. This research benefits not only those with motor disorders but also athletes, offering insights to improve training and rehabilitation. Ultimately, this work promises to revolutionize neurology and rehabilitation treatments, benefiting patients and athletes alike by bridging clinical and performance contexts.

2 Band origin and mechanisms of neural oscillations in the beta frequency band

Beta oscillations, typically ranging from 13 to 30 Hz, are observed in numerous perceptual, cognitive, and motor processes (Brovelli et al., 2004; Witham et al., 2007). These oscillations are involved in diverse behavioral paradigms, including sensorimotor integration, coordination, idle-state processing, motor preparation, and attention. Given the intricate nature of Beta-oscillation activity, their origins are likely rooted in complex and varied mechanisms (Pfurtscheller et al., 1997; Kilavik et al., 2013; Shin et al., 2017; Spitzer and Haegens, 2017; Betti et al., 2021).

2.1 Distribution of beta oscillations across key brain regions

Beta-band neural oscillations are predominantly found in brain regions associated with the sensorimotor system, notably in the precentral gyrus (Hari and Salmelin, 1997), supplementary motor area, cingulate cortex, and dorsolateral prefrontal cortex (Sochurková et al., 2006). These oscillations are also observed in the sensorimotor and premotor cortices, parietal lobes, and cerebellum (Fujioka et al., 2015), basal ganglia as well as in the various muscle locations (Baker, 2007; De Marchis et al., 2015; Rana et al., 2015; Reyes et al., 2017), the spinal cord (as evidenced in primates) (Oya et al., 2020), the dorsal root ganglia (Baker et al., 2006), and peripheral motor units (Blenkinsop et al., 2017). Beta oscillations are involved in all motor control-related systems, indicating their significant role in the overall functionality of the motor system.

Typically, beta oscillations are present during stable motor states and decrease during movement. The variations in beta oscillations during motor-related neurophysiological processes are often attributed to the synchronized activity of neurons in specific local areas of the motor cortex (Espenhahn et al., 2017; Barone and Rossiter, 2021). This phenomenon has been observed in multiple studies, where motor-related beta decrease (MRBD) and post-movement beta rebound (PMBR) are considered classic examples of event-related desynchronization/synchronization (ERD/S) (Stancák and Pfurtscheller, 1995; Byrne et al., 2017). Figure 1 illustrates PMBR/MRBD. These phenomena reflect the complex neural regulatory mechanisms involved in motor execution and control. The stability of these changes appears consistent across different effectors, types of movement, speeds, complexities of movement, and age groups (Kilavik et al., 2013).

2.2 Regional characteristics and mechanisms of beta oscillations in EEG

Beta oscillations in EEG signals can be categorized into Rolandic beta and Frontal beta, each exhibiting distinct regional characteristics and functional associations. Frontal beta rhythm generally displays maximal power in the frontal lobe areas and is associated with cognitive tasks such as stimulus evaluation and decision-making (Stoll et al., 2015; Schmidt et al., 2019). In contrast, Rolandic beta rhythm exhibits its greatest power in the sensorimotor regions and is linked with tasks involving motor imagery, motor preparation, and motor execution (Pfurtscheller and Solis-Escalante, 2009; Brinkman et al., 2014; Nijhuis et al., 2021). Often termed the Rolandic beta indicates a "resting state" of brain activity (Pfurtscheller et al., 1996a; Fairhall et al., 2007; Ritter et al., 2009), where its presence during rest negatively correlates with heart rate variability (Triggiani et al., 2016). This rhythm becomes particularly active during motor preparation and execution, showing a negative correlation with the timing of motor decisions (Jo et al., 2016).

2.3 Types and mechanisms of beta oscillations

Initial studies identified two main types of Beta-oscillations: one associated with the μ-rhythm, ~22–24 Hz, showing desynchronization (Event-Related Desynchronization, ERD) before and during movement, and slow synchronization recovery post-movement. The other type, post-movement beta synchronization (PMBS), starts to desynchronize shortly before movement and rapidly resynchronizes afterward, lasting about 1–2 s, predominantly within the 12–26 Hz frequency range and showing contralateral dominance (Pfurtscheller, 1981;

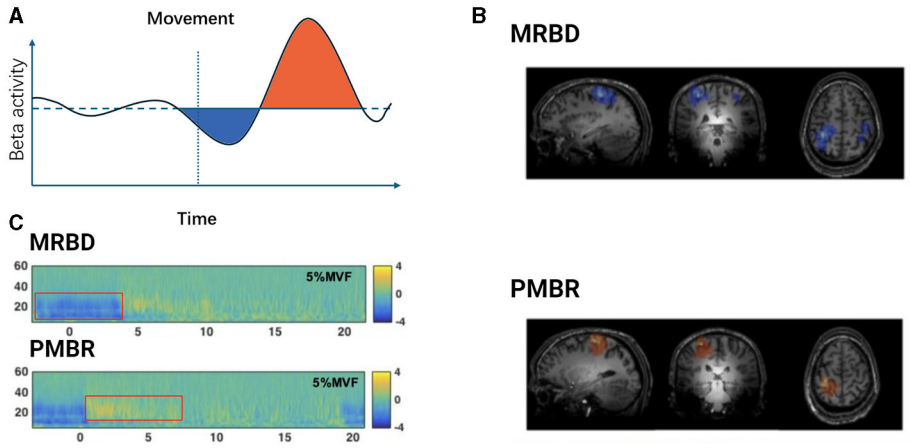

FIGURE 1
Temporal dynamics of beta oscillations during movement execution. **(A)** Schematic representation of Beta activity dynamics during motor tasks. The light blue shaded area indicates the period of Movement-Related Beta Desynchronization (MRBD) occurring before and during movement execution. The light purple shaded area represents the Post-Movement Beta Rebound (PMBR), which increases swiftly after task completion and slowly returns to baseline levels. **(B)** Spatial features of MRBD (top) and PMBR (bottom) in an individual participant. Adapted from Seedat et al. (2020). **(C)** Time-frequency spectra extracted at peak locations during a 5% Maximum Voluntary Force (MVF) isometric wrist flexion task, depicting MRBD (top) and PMBR (bottom). Adapted from Fry et al. (2016).

Pfurtscheller et al., 1997). Differential Beta frequencies in cortical hand and foot areas suggest variations in neural network structures and interconnectivity across specific sensorimotor cortical regions, indicating that different Beta oscillations may be specific to different motor areas (Pfurtscheller et al., 2000; Neuper and Pfurtscheller, 2001). Current research often divides Beta-band oscillations into lower and higher frequency bands, using 20 Hz as a demarcation line (Engel and Fries, 2010; Saleh et al., 2010; Schmidt et al., 2019).

Beta oscillations, particularly Beta1 (≈15 Hz) oscillations, were first identified in experimental and modeling studies within the association area of the cerebral cortex in rats (Kramer et al., 2008). These rhythms are thought to form through the interaction and temporal coordination between deep and superficial cortical cells, becoming prominent after transient excitatory (sensory) inputs are removed (Roopun et al., 2008). The sustainability of this rhythm does not depend on synaptic plasticity but is determined by the cells' response to inhibitory rebound, allowing these assemblies to sustain themselves by responding to both familiar and novel stimuli (Whittington et al., 2000).

Beta2 (20–30 Hz) oscillations are thought to originate within non-synaptic networks of layer V pyramidal cells, which contribute to the corticospinal tract. These oscillations rely on gap junction coupling and can persist even when layer IV is removed, suggesting they do not depend on apical dendritic electrogenesis (Roopun et al., 2006). M-type K+ currents are believed to determine the oscillatory period, suggesting that cortical network oscillations under normal conditions may predominantly arise from non-synaptic mechanisms.

Furthermore, the experimental models illustrate that beta activity can facilitate inter-layer and intra-layer interactions, where groups of neurons synchronized within the beta band can coexist with other cell groups (Kilavik et al., 2013). Beta oscillations have complex generation mechanisms and unique anti-dynamics properties (Donoghue et al., 2022), allowing them to persist long after excitatory inputs have decayed (Kopell et al., 2011). This diverse neural oscillatory rhythm is likely closely related to broader endogenous top-down processing and sensorimotor integration, as discussed by Barone and Rossiter (2021). Additionally, in motor control processes, there is a quantifiable relationship between local concentrations of gamma-aminobutyric acid (GABA) and beta amplitude (Hall et al., 2011; Muthukumaraswamy et al., 2013; Rossiter et al., 2014), with high-frequency beta2 oscillations possibly playing a significant role. The generation of sensorimotor beta oscillations is thought to be regulated by phase-locked GABA-mediated interneuronal inputs associated with the activity of layer V pyramidal cells (Baker, 2007; Gaetz et al., 2011). Computational neural models suggest that layer V pyramidal cells exhibit alternating depolarization and hyperpolarization, an interaction that triggers sensorimotor beta oscillations (Baker, 2007; Bhatt et al., 2016; Wischnewski et al., 2022). Therefore, subsequent research often links changes in motor cortex beta oscillations with variations in GABA, and associated changes in cortical inhibition and plasticity.

Firstly, beta oscillations play a crucial regulatory role in motor control by coordinating neuronal synchronization, which ensures the precise transmission and execution of motor commands. Secondly, the relationship between local gamma-aminobutyric acid (GABA) concentrations and beta amplitude indicates that GABA significantly influences motor function, directly affecting motor control and coordination. Additionally, beta oscillations are involved in sensorimotor integration, suggesting that the brain utilizes these oscillations to coordinate sensory input and motor output, thereby ensuring the accuracy and fluidity of movements. In terms of neural plasticity, beta oscillations are associated with changes in cortical inhibition and plasticity, which are essential for motor learning and adaptation, particularly in the acquisition of new motor skills. Finally, computational neural models propose that alternating depolarization and hyperpolarization of layer V pyramidal cells trigger sensorimotor beta oscillations. This

mechanism provides a theoretical foundation for understanding the neural processes underlying motor control and may contribute to the development of novel treatments for motor disorders.

2.4 Mechanisms of abnormal beta oscillations

In Parkinson's disease, beta frequency oscillations in the basal ganglia and cortex may originate from inhibitory interactions between medium spiny neurons in the striatum. McCarthy et al. (2011) found through mathematical modeling and experimental observations that amplification of striatal network dynamics could enhance beta frequency oscillations. When a cholinergic agonist was injected into the striatum of normal, awake animals, significant beta frequency oscillations were observed, aligning with model predictions. These oscillations were linked to synaptic GABAa currents and intracellular M currents, promoting collective beta frequency oscillations (Shimono et al., 2000; Deffains and Bergman, 2015; Kondabolu et al., 2016).

The mechanisms underlying beta oscillations are not fully understood, with hypotheses proposing both cortical and subcortical origins. Cortical genesis theories, supported by *in vitro* studies, suggest potential pathways involving transmission from superficial to deep layers of pyramidal cells (Bollimunta et al., 2008). These studies indicate that the activation of deep pyramidal cell layers or synchronized hyperpolarization across layers can induce Beta-oscillations (Weiler et al., 2008; Bhatt et al., 2016). Biophysical modeling predicts that high-amplitude beta bursts in human motor and sensory cortices may originate from temporally aligned excitatory synaptic drives across deep and superficial layers (Bonaiuto et al., 2021). Different mechanisms of beta generation are illustrated in Figure 2.

Subcortical theories focus on the basal ganglia, particularly the STN-GPe loop within the striato-thalamo-cortical circuitry (Holgado et al., 2010). Chronic dopamine depletion in Parkinson's disease may reorganize the cortico-basal ganglia-thalamo-cortical (CBGT) circuit. However, these models, which involve changes in connections from the cortex to subthalamic nuclei and from the STN to the external globus pallidus, have not yielded unanimous results. Liu et al. (2020) proposed a dual-oscillator system encompassing the BG-Th network and the cortex, capable of generating high or low-frequency Beta1 or Beta2 oscillations depending on the structure of the oscillators, suggesting a possible theory for the multiple origins of Beta-oscillations.

3 Functional roles of beta oscillations

Neural oscillations are a hallmark of brain network information processing (Han et al., 2021a,b), yet a consistent one-to-one mapping between these oscillations and brain network activities does not seem to exist (Doelling and Assaneo, 2021; Lundqvist and Wutz, 2022). Although many studies have observed correlations between neural activity and other physiological signals, beta oscillations appear to be specifically related to task-relevant information (Spitzer and Haegens, 2017). This includes the generation of motor goals (Fischer et al., 2017), maintenance and monitoring of tasks and states (Shin et al., 2017; Little et al., 2018), and learning and adaptation to motor-related errors (Pollok et al., 2014; Wang et al., 2019). Complex brain network activities in different states affect the amplitude, frequency, timing, and distribution of beta oscillations (Schmidt et al., 2019).

3.1 Functional roles of beta oscillations and task-specific information processing

Historically, some researchers believed that beta oscillations might reflect a concept where the motor system is in an "idling" state (Pfurtscheller et al., 1996a; Kilavik et al., 2013), representing the processing of motor-related sensory information (Salmelin and Hari, 1994). However, increasing evidence suggests that the "idling" concept does not fully explain the function of beta oscillations in sensorimotor activities. Instead, beta oscillations are likely involved in maintaining the current sensorimotor or cognitive state (Pfurtscheller et al., 1996b; Fairhall et al., 2007), rather than merely reflecting the motor system's idle state. For instance, Cassim's study showed that ischemia-induced reduction in incoming sensory feedback led to the disappearance of beta oscillations, broadening our understanding of their role in the sensorimotor system beyond merely "idling" (Cassim et al., 2001). Beta oscillations not only facilitate the stabilization of movements but also influence the generation of new movements (Engel and Fries, 2010). They are more pronounced in processing unattended stimuli and during motor-related anticipatory processes, such as when compensating for expected disturbances or maintaining a specific motor state (Caetano et al., 2007). This reflects top-down control signals used to suppress irrelevant information or disturbances and regulate the motor system (Gilbertson et al., 2005).

3.1.1 Gating mechanisms of beta oscillations in sensorimotor processing

As proposed by Jensen and Mazaheri, the "gating theory" suggests that information is transmitted by functionally blocking pathways unrelated to the task at hand. Through inhibitory gating, beta oscillations primarily involve gating in the somatosensory cortex by suppressing upcoming sensorimotor transformations across different cortical activity bands (Jensen and Mazaheri, 2010; Talsma et al., 2010). Stevenson et al. viewed beta oscillations as a form of local cortical gating aimed at facilitating complex neural activities, such as information processing. In some circumstances, local neurons may reduce beta amplitude to accommodate more complex neural activities, as observed by Schulz et al., where motor-related beta suppression (ERD) coincided with enhanced muscle coupling within the alpha band, and beta rebound (ERS) was associated with reduced muscle coupling. This confirms that enhancements in Beta-band oscillations reflect stabilization or inhibitory mechanisms of the motor system, hindering the activation or selection of new motor behaviors (Schulz et al., 2013). Consistent findings have been observed in human magnetoencephalography during attention tasks and in local field potentials in mice performing execution detection tasks, indicating that an increase in beta oscillations signals reduced

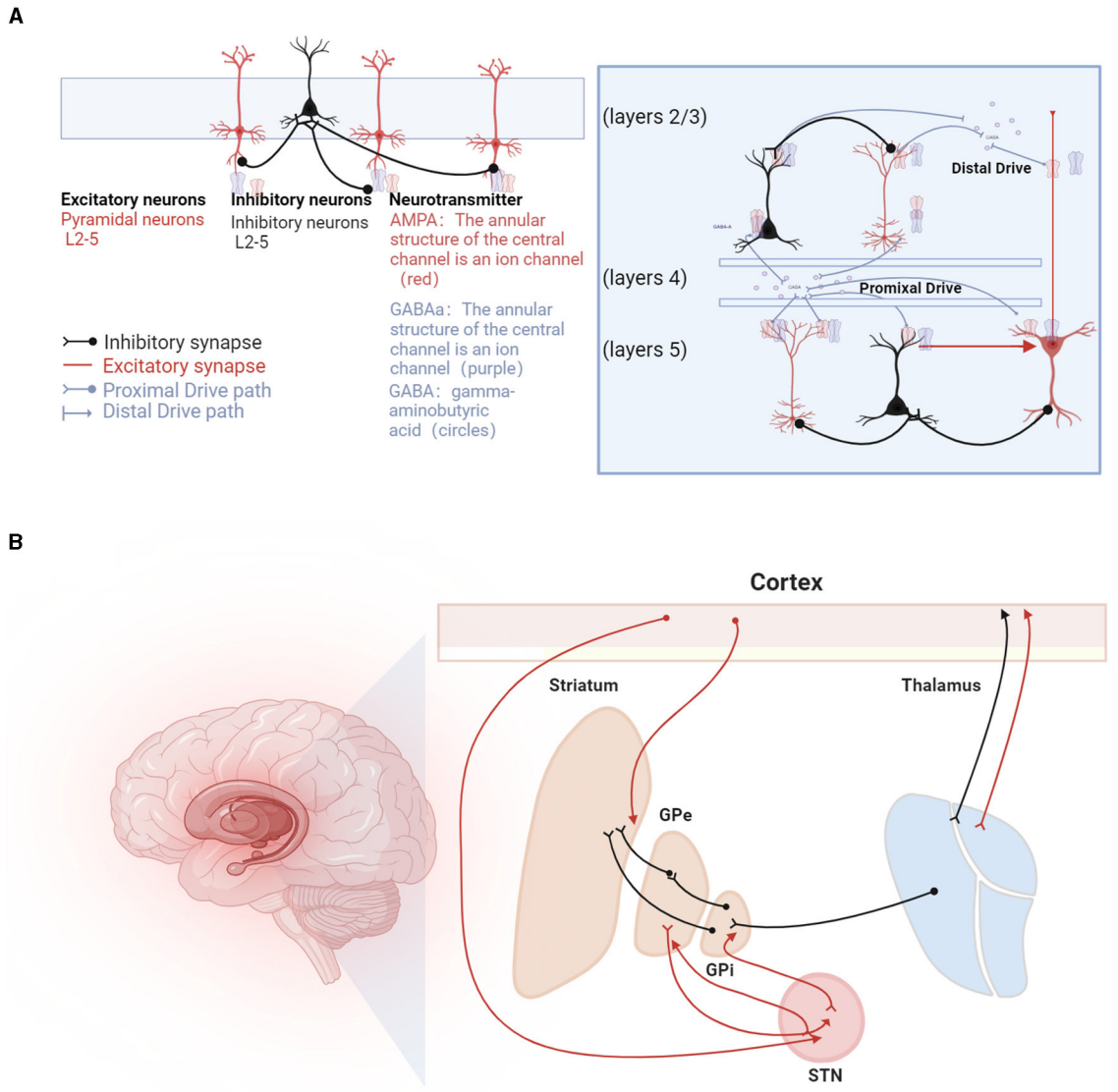

FIGURE 2
Beta oscillations in the sensorimotor system. **(A)** Illustration of the mechanisms underlying beta oscillation generation. On the left, beta oscillations are depicted as arising from recurrent interactions within deep cortical layers (Lacey et al., 2014), involving pyramidal neurons (represented as red triangles) and interneurons (depicted as green circles). GABA (gamma-aminobutyric acid) is shown as circles, with GABAa receptors forming the annular structure of a central ion channel (purple), and AMPA receptors, also forming a central ion channel structure (red), primarily facilitate rapid excitatory transmission, while GABAa receptors are mainly responsible for rapid inhibitory transmission. At the center, a laminar model displays beta generation facilitated by pyramidal neurons located in both supragranular (layers 2/3) and infragranular layers (layer 5), influenced by dual external excitatory inputs, predominantly from the thalamus (Sherman et al., 2016). Additionally, beta bursts are generated by a model incorporating a broad proximal excitatory synaptic drive synchronized with a strong distal synaptic drive (Bonaiuto et al., 2021). **(B)** Hypotheses regarding the generation of beta rhythms in the basal ganglia pathways, involving inhibitory and excitatory circuits: (1) STN-GPe Rhythm Hypothesis: Beta oscillations originate from the network interactions between the subthalamic nucleus (STN) and the external globus pallidus (GPe). (2) Cortical Origin Hypothesis: In Parkinson's disease (PD) patients, beta oscillations are thought to originate from the cortical-basal ganglia-thalamocortical loop. (3) Striatal Origin Theory: Enhanced beta rhythms result from increased inhibitory interactions among striatal neurons. (4) Integrated Neural Circuit Changes Theory: Excessive beta rhythms are hypothesized to arise from a composite effect of inherent neuronal properties within the cortical-basal ganglia-thalamocortical loop and its associated circuits (not listed).

efficiency in information transmission (Shin et al., 2017). This also explains why extensive studies have noted motor-related beta decrease (MRBD) before movement, and post-movement beta rebound (PMBR) associated with suppressed somatosensory processing and sensory input to motor actions (Stevenson et al., 2011; Limanowski et al., 2020). According to this hypothesis, more complex neural activities, such as motor planning and execution, monopolize neural resources. Similar phenomena occur during imagined and observed movements (Kilavik et al., 2013; Buchholz et al., 2014).

3.1.2 Cognitive processing and beta oscillations in motor actions

Motor processes are dynamically regulated through coordination between cognitive processing in the brain and the motor system (Brisswalter et al., 2002). Complex motor actions involve cognitive decisions and judgments, and brain regions associated with these functions have also been reported to exhibit beta oscillation activity (Koelewijn et al., 2008; Alayrangues et al., 2019). Lundqvist et al. (2011, 2016, 2018) reported an increase in theta and gamma power with increased working memory load, alongside a decrease in alpha/beta power, indicating the involvement of beta oscillations in cognitive functions, particularly working memory. Experiments on motor anticipation and selection of specific objects have revealed the potential role of beta oscillations in flexibly controlling working memory (Lundqvist et al., 2018). The functionality of beta oscillations related to working memory in the prefrontal cortex (PFC) has been extensively discussed, highlighting their significance in cognitive control mechanisms (Schmidt et al., 2019).

It is noteworthy that, during sustained isometric contraction tasks, the short "burst" characteristics of neural oscillations and connectivity between the brain and muscles have been observed (Echeverria-Altuna et al., 2022). Analyzing neural oscillations as a series of transient burst events rather than continuous oscillatory activities offers an exciting new perspective (van Ede et al., 2018; Doelling and Assaneo, 2021; Rayson et al., 2023). The intermittent, transient, high-power burst events observed during various neural activities are also significant; analyzing these events across different dimensions of time, spectrum, and space presents challenges and is crucial for accurately describing event characteristics and revealing their interactions (Zich et al., 2020; Doelling and Assaneo, 2021). This approach enhances our understanding of brain dynamics across different tasks and cognitive states, enabling the capture of non-periodic features of the brain that aid in elucidating its role in various cognitive functions such as attention, memory, and consciousness. This advancement further propels our understanding of neural oscillations. Further insights into beta oscillations during the stages of information encoding, retrieval, and selective deletion have been provided by previous studies. Cross-regional interaction studies have highlighted the crucial role of beta oscillations in coordinating brain networks during both task execution and resting states, with additional discussions on their involvement in cognitive processing (Lundqvist et al., 2024). Investigating the neural circuit origins of beta bursts, their shared mechanisms in cognition and action stopping, and the potential of beta burst analysis to enhance the diagnosis and treatment of neurological diseases remain pivotal areas for future research.

The activity in the beta frequency band holds significant biomarker potential within the sensorimotor system, particularly in pathological contexts. Given the complex composition of the motor system, the effects of different motor parameters on beta oscillations and their role in brain-muscle communication require further investigation and validation. The modulation of brain oscillation power may be closely related to the degree of spike synchronization and the balance between excitatory and inhibitory signals within the neuronal network (Buzsáki and Draguhn, 2004; Han et al., 2023b). Therefore, oscillations at different frequencies might reflect distinct states of neuronal clusters or networks. To establish a strong link between oscillations and behavior, it is essential to explore how these oscillations reflect and drive underlying neural activity (Kirschstein and Köhling, 2009). This deeper understanding will not only enhance our comprehension of the functional dynamics within the sensorimotor system but also improve our ability to effectively address motor system dysfunctions.

4 Beta oscillations in the context of corticomuscular coherence

4.1 Characteristics and functions of beta oscillations within the CMC context

The study of functional connectivity between the cerebral cortex and muscles during motor states effectively models changes in brain networks (Schulz et al., 2013). Motor commands issued from the motor cortex lead to muscle contractions through efferent motor pathways and are modulated by afferent somatosensory pathways (Schomburg, 1990; Rijntjes et al., 1999). The functional coupling of electrophysiological signals between the cortex and muscles, known as corticomuscular coupling, is typically measured using corticomuscular coherence (CMC). serves as a biomarker for corticomuscular connectivity, providing insights into cortical control of muscle function (Fauvet et al., 2021).

Electrophysiological techniques such as EEG, MEG, ECoG, and intracranial electrode recordings offer millisecond-level temporal resolution, advancing our understanding of neural oscillations (Kirschstein and Köhling, 2009; Baillet, 2017; Han et al., 2022, 2023a; Lin et al., 2024; Wang B. et al., 2024). These technologies enable real-time tracking of neural signals, revealing the dynamics of neural activity (Lundqvist and Wutz, 2022). CMC reflects the activity of sensorimotor networks during dynamic movements and isometric contractions, useful for diagnosing and rehabilitating movement disorders (Airaksinen et al., 2015; Liu et al., 2019a). A key challenge in neurophysiology is understanding the synchronization between EEG and EMG signals, which constitutes CMC (Kasuga et al., 2018). Conway et al. (1995, 2004) discovered significant beta band coherence (13–35 Hz) between cortical activity and EMG of contralateral hand muscles, indicating synchronized cortical neuronal activity relates to motor unit firing. CMC is most commonly observed during isometric contractions and is associated with stable force output, primarily in the beta frequency band (15–30 Hz). This coupling of information between the cortex and muscles, predominantly found in the beta frequency band (15–30 Hz) (Mima et al., 2002; Engel and Fries, 2010; Mehrkanoon et al., 2014). The pathways mediating corticomuscular coupling are illustrated in Figure 3.

4.2 Coherence measurement and analytical techniques in beta-CMC

Coherence measures the linear connection between two signals in the frequency domain. In CMC, it assesses the synchrony between brain activity, recorded via electroencephalography (EEG),

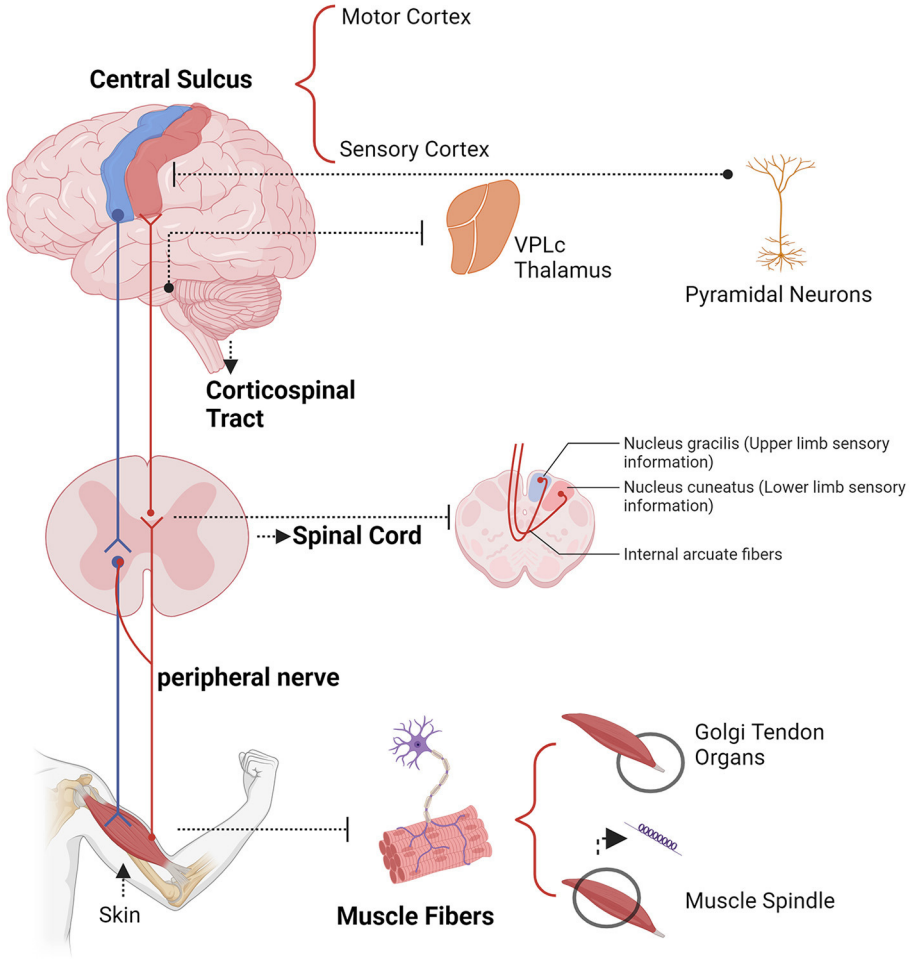

FIGURE 3
Example descending (blue) and ascending (yellow) pathways which could mediate corticomuscular coherence.

and muscle activity, recorded via electromyography (EMG). The coherence between EEG and EMG signals is calculated using the normalized cross-spectrum density:

$$\mathrm{Coh}_{\mathrm{EEG,EMG}}(\mathrm{f}) = \frac{\left|P_{EEG,EMG}(f)\right|^2}{\mathrm{P}_{\mathrm{EEG}}(\mathrm{f}) \cdot \mathrm{P}_{\mathrm{EMG}}(\mathrm{f})}$$

where $(P_{EEG,EMG}(f))$ is the cross-power spectrum of the EEG and EMG signals at frequency (f), and $(P_{EEG}(f))$ and $(P_{EMG}(f))$ are the power spectra of the EEG and EMG signals at frequency f, respectively. Coherence values range from 0 to 1, with higher values indicating a stronger correlation between the two signals (Mima et al., 1999). High coherence at specific frequencies suggests robust neural communication from the cortex to the muscles, indicating effective corticospinal pathways.

CMC is crucial for understanding motor control mechanisms, particularly in movement disorders and rehabilitation strategies. It dynamically adjusts with muscle contraction patterns, reflecting top-down motor information transmission (Baker et al., 1997; Brown et al., 1998; Mima et al., 1999; Ushiyama et al., 2012; Boonstra, 2013).

Initial methods for CMC analysis involved Fourier coherence and partial directed coherence (Grosse et al., 2002; Schelter et al., 2006; Yao et al., 2007). Both methods handle non-stationary signals; however, wavelet coherence, with its fixed window size, adapts better to the frequency of oscillatory signals, providing more accurate results. Partial directed coherence evaluates the direction of neural information flow, offering insights into the functional connection between cortical and muscular signals. Wavelet coherence has become widely adopted due to its ability to handle non-stationary signals and provide time-frequency localized information (Yang et al., 2010; Xi et al., 2021).

To further advance CMC analysis, researchers have explored various dimensions such as local frequency bands, cross-frequency coupling, time delays, and multiscale characteristics. Functional corticomuscular coupling (FCMC), essentially another term for CMC, was first introduced by Yang et al. (2009). Functional corticomuscular coupling (FCMC) probes multi-level information communication in the sensorimotor system (Ibáñez et al., 2021). Traditional methods like canonical coherence (caCOH) have been used to measure FCMC between multivariate signals at a single scale (Vidaurre et al., 2019).

Recent advancements propose multiscale canonical coherence (MS-caCOH) to disentangle complex multi-layer information across multiple scales, demonstrating enhanced coupling detection and lower pattern recovery errors (Sun et al., 2024). Similarly, composite multiscale coherence (CMSC) models explore FCMC in motor control systems, showing stability at high time scales and capturing multiscale characteristics with higher coherence in alpha and beta bands (Chen et al., 2023). These methods extend FCMC research by offering robust and detailed multiscale interaction analysis. In addition to these methods, advanced techniques such as multiscale transfer entropy (MSTSE) have been introduced to describe multi-layer neural information transfer between coupling signals (Xi et al., 2022). MSTSE is more robust and effective in detecting coupling properties compared to single-scale methods, allowing for the analysis of FCMC at various scales and frequencies, providing a comprehensive understanding of the multi-scale characteristics of FCMC (Sun et al., 2024).

Studies have also revealed nonlinear properties in the sensorimotor control loop. Linear coupling is primarily driven by descending motor pathways, while afferent sensory feedback contributes to nonlinear coupling patterns (Myers et al., 2003; Yang et al., 2018; Liang et al., 2020). The integration of nonlinear coupling algorithms and advanced modeling techniques continues to enhance our understanding of the neural mechanisms underlying CMC, facilitating the identification of factors affecting CMC.

There is ongoing debate regarding the rectification of EMG in CMC calculations (Yoshitake and Shinohara, 2013; McClelland et al., 2014). While rectification is often used to maximize information about action potential timing and suppress information related to motor unit action potential (MUAP) shape, some studies suggest that it does not enhance the detection of CMC. Rectification can distort the EMG spectrum and obscure genuine CMC detection in some cases (Neto et al., 2010). Therefore, it is argued that coherence analysis should be performed using unrectified EMG to avoid these issues (McClelland et al., 2012). This perspective highlights the need for careful consideration of preprocessing steps in CMC analysis to ensure accurate and reliable results.

4.3 Beta-CMC in different motor tasks

4.3.1 Beta-CMC in stable motor states

In this section, the term "stable motor states" refers specifically to motor conditions designed to minimize interference from electromyographic (EMG) noise. These stable conditions include single-joint movements, isometric contractions, and other controlled motor tasks that reduce muscle activity artifacts. By focusing on these stable states, researchers can better isolate and study the underlying neural mechanisms of Beta-band corticomuscular coherence (CMC) without the confounding effects of more complex, multi-joint movements. This approach ensures that the observed CMC reflects true corticospinal communication rather than extraneous muscle activity.

Beta-CMC disappears before the start of a movement and increases during isometric contractions with low-level static force adjustments, potentially stabilizing corticospinal information exchange (Chakarov et al., 2009). During dynamic force output, it is replaced by transient synchronization in the alpha and gamma bands, with phase synchronization in different frequency bands indicating incoming and outgoing corticospinal interactions (Mehrkanoon et al., 2014). Changes in Beta-CMC under different motor tasks or states are summarized in Table 1. Bottom-up Beta-band activity may facilitate steady isometric contractions by effectively transmitting sensory feedback from the finger muscles to the sensorimotor cortex (Lim et al., 2014). Changes in CMC phase induced by cooling the arm (Riddle and Baker, 2005) and ischemia-induced reductions in afferent nerve capability (Pohja and Salenius, 2003) have demonstrated the role of incoming peripheral sensory signals in sensorimotor communication. Thus, CMC is considered to be regulated by top-down motor commands and feedback signals from proprioceptors, which also modulate this (Budini et al., 2014). Interestingly, pharmacological studies have shown that enhancements in EEG signals by benzodiazepines do not modulate the amplitude of CMC (Baker and Baker, 2003), while various types of GABAergic medications produce diverse modulations of cortical activity and CMC amplitude (Barone and Rossiter, 2021).

What is the connection between widely observed Beta-CMC and movement during stable motor processes? Prior to the initiation of movement, a reduction in beta power is associated with faster autonomous movements (Gilbertson et al., 2005; Shin et al., 2017). When the amplitude of Beta-CMC increases, the generation of new movements is delayed (Matsuya et al., 2013), and prolonged elevated beta oscillations have been observed in Parkinson's disease, associated with difficulties in initiating and controlling movements (Brown, 2006; Asadi et al., 2022).

These findings suggest that the mechanisms underlying CMC are complex and not merely a simple unidirectional transmission phenomenon. Instead, they involve a complex interplay of motor commands and sensory feedback. This coherence relates to sensorimotor integration functions (Kilavik et al., 2013), indicating a comprehensive and mutually regulatory relationship between motor commands and sensory feedback (Witham et al., 2011).

4.3.2 Beta-band CMC across dynamic motor states

Significant Beta-CMC has been observed in human standing tasks, highlighting the cerebral cortex's role in maintaining balance and responding to changes in mechanical and sensory conditions (Jacobs et al., 2015). However, due to the subtle and unstable nature of EEG signals, few studies have explored limb CMC during large-amplitude movements (Gennaro and De Bruin, 2018; Zhao et al., 2022a). This section focuses on the role of Beta-Band CMC across various dynamic motor states, emphasizing the impact of large-amplitude movements on EEG signals.

Jensen et al. (2019) investigated CMC during treadmill walking, finding significant beta and gamma band coherence between EEG and EMG signals from the tibialis anterior and soleus muscles during the stance and propulsion phases of gait. Directional analysis showed EEG activity led EMG activity during the support phase and forward propulsion (Jensen et al., 2019). Similarly,

TABLE 1 Summary of Beta-band corticomuscular coherence (Beta-CMC) changes under different conditions.

Condition	Beta-CMC changes	References
Stable motor states		
Isometric contraction tasks	Significant Beta-CMC observed, indicating the cerebral cortex's role in maintaining balance and stability	Jacobs et al., 2015; Liu et al., 2019b
Isokinetic contraction tasks	CMC differences disappear, suggesting a shift from feedforward to feedback regulation in motor control	Liu et al., 2019b; Suzuki and Ushiyama, 2020
Different motor states		
Large amplitude movement states	Few studies due to the subtle and unstable nature of EEG signals, limiting exploration of limb CMC	Gennaro and de Bruin, 2020; Kenville et al., 2020; Xi et al., 2022
Treadmill walking	Significant beta and gamma band coherence between EEG and EMG signals from the tibialis anterior and soleus muscles during stance and propulsion phases	Jensen et al., 2019; Gennaro and de Bruin, 2020
Ground walking during double-support phase	Higher Beta-CMC observed, with EEG signals preceding EMG signals, indicating cortical activity leads muscle activity	Roeder et al., 2018
Periodic bilateral ankle movements	Increased coherence near 20 Hz, primarily in brain regions directly controlling the tibialis anterior and soleus muscles; coherence enhanced with external rhythmic guidance	Yoshida et al., 2017
Different task conditions and force levels	CMC exhibits different patterns; decreases with increased contraction intensity during intermittent elastic tasks, but differences disappear in sustained isometric tasks	Suzuki and Ushiyama, 2020
Sensorimotor integration		
External sensory feedback (visual, auditory)	Changes in sensory feedback (e.g., reduced visual feedback) lower Beta-CMC peak frequency, indicating the influence of sensory inputs on CMC	Chung et al., 2017; Chen et al., 2023

Roeder et al. (2018) reported higher CMC during the double-support phase of ground walking, with EEG signals preceding EMG signals. These findings suggest a crucial role for Beta-CMC in coordinating complex motor tasks.

In neuromuscular coupling research during gait, involving both healthy individuals and those with neuromuscular or nervous system diseases, the synchronicity between EEG and EMG signals, defined as Neuromuscular Connectivity (NMC), has been explored (Zhao et al., 2022b). While NMC holds significant potential for assessing brain-muscle interactions, there is a need for standardizing research methodologies to enhance comparability and reproducibility (Zhao et al., 2022b; Seynaeve et al., 2024).

Yoshida et al. found that during periodic bilateral ankle movements, brain regions controlling movement showed increased coherence near 20 Hz with the tibialis anterior and soleus muscles. This coordination intensified with external rhythmic guidance, enhancing focus on movement (Yoshida et al., 2017). Beta-band activity dynamically adjusts to motor task demands, indicating that neural synchronization and connectivity may involve brief "bursts" rather than continuous states (Mirzaei et al., 2017).

The generation of beta oscillations varies with different activities. Khanna and Carmena noted that beta activity is commonly produced in the striatum during significant external stimuli, adjusting internally planned actions. During static isometric contractions, beta activity relates to autonomous contractions, involving pyramidal tract neurons discharging in the beta range, which increases motor neuron activity and muscle force production (Khanna and Carmena, 2017). Thus, beta oscillations are linked to action planning, muscle coordination, and force production, reflecting how the brain regulates these processes (Iwama et al., 2022), and physiologically reflect how the brain regulates coordination among different muscles.

While these findings provide valuable insights, there are limitations. The instability of EEG signals poses challenges in studying large amplitude movements. Future research should focus on standardizing NMC methodologies and exploring new techniques to overcome these limitations. Understanding the dynamic interactions between cortical regions and muscles across various motor tasks will enhance our knowledge of sensorimotor integration and inform more precise interventions for motor disorders.

4.3.3 Beta-band CMC in force control and precision movements

Beta-CMC is prominently observed during stable isometric contractions. While some studies suggest that Beta- does not significantly vary with motor parameters such as movement speed and accuracy (Kilavik et al., 2013; Dal Maso et al., 2017), other research indicates a positive correlation between Beta- amplitude and movement precision. For instance, during a pinch grip task, Beta- reflects a synergistic control strategy, integrating task-relevant motor neurons into functional units (Reyes et al., 2017).

Studies have shown a positive correlation between Beta-CMC amplitude and movement precision. Under dual-task conditions, where attentional resources are divided, CMC amplitude decreases, yet higher-frequency Beta-CMC is associated with greater precision in motor tasks (Kristeva-Feige et al., 2002; Kristeva et al., 2007).

Conversely, Johnson found that additional tasks reduce Beta-CMC, highlighting the impact of divided attention on

corticomuscular coupling (Johnson et al., 2011). Further research has indicated that internal focus during tasks can decrease Beta-CMC and impair force accuracy and stability (Parr et al., 2023a). For example, when one hand is engaged in medium strength contractions, the other hand shows increased CMC due to extensive bilateral cortical connections (Zheng et al., 2016). This suggests that attentional demands significantly influence Beta-CMC.

Divekar explored differences between wrist flexors and extensors, finding that frequent use and lower perceptual difficulty of wrist flexors lead to better adaptation and lower CMC levels during isometric tasks (Divekar, 2013). Precise motor control is linked to bilateral supplementary motor area (SMA) activity, with SMA projections to the corticospinal tract becoming significant for high-precision tasks (Matsuya et al., 2013). Desmyttere's study reported that co-activation of synergistic muscles decreases Beta-CMC, while antagonist muscle activation increases it, suggesting a role in fine motor control (Desmyttere et al., 2018). Averbeck hypothesized that coherent oscillations between neurons reflect dynamic information flow, with steady-state CMC being suboptimal under unpredictable force conditions (Averbeck and Lee, 2004; Mendez-Balbuena et al., 2012).

Ushiyama found that CMC decreases with increasing contraction intensity during intermittent elastic tasks but not in sustained isometric tasks, indicating context-dependent modulation (Suzuki and Ushiyama, 2020). These findings suggest that Beta-CMC reflects a shift from feedforward to feedback regulation in motor control, influenced by factors such as force magnitude, attention, and task complexity (Lattari et al., 2010).

The information highlights the complexity and context-dependency of Beta-CMC. Beta-CMC is crucial for maintaining stable muscle force during isometric contractions, but its relationship with motor parameters like movement speed and accuracy is less consistent. Attention significantly affects Beta-CMC, with divided attention reducing its amplitude, while higher-frequency Beta-CMC is linked to greater motor precision. Beta-CMC's dynamic adjustment underscores the complexity of corticomuscular connections. It exhibits different patterns under varying task conditions and force levels. For example, Beta-CMC decreases with increased contraction intensity during intermittent elastic tasks, but this difference disappears in sustained isometric tasks. This context-dependent modulation suggests Beta-CMC reflects a shift from feedforward to feedback regulation in motor control. Additionally, sensory feedback and common inputs are crucial for CMC, requiring further experimental validation.

Future research should explore the interactions between different cortical regions and muscle groups across various motor tasks, incorporating both intermuscular coherence (IMC) and CMC to understand broader neural network dynamics. This will provide insights into how the brain controls muscle activity and adapts to different motor demands, potentially leading to more precise interventions for motor disorders.

4.3.4 Beta-band CMC in sensorimotor integration

The sensorimotor cortex continuously processes dynamic stimuli from the environment, crucially regulating autonomous movements (Hohlefeld et al., 2011; Piitulainen et al., 2021). Primates can spontaneously synchronize with environmental rhythms, and these stimuli modulate Beta-CMC (Lattari et al., 2010; Piitulainen et al., 2015; Wang G. et al., 2024). This modulation occurs in areas such as the basal ganglia, cerebellum, SMA, pre-SMA, and PMC, dynamically adjusting to external stimuli (Saleh et al., 2010; Fujioka et al., 2012). Varlet et al. (2020) found that Beta-CMC plays a role in the synchronization of movements with 2 Hz audio-visual sequences, indicating its potential mechanism for movement synchronization.

Rhythmic structure perception in the brain extends beyond auditory areas to involve the sensorimotor cortex, basal ganglia, and hippocampus. During metronome listening, non-phase-locked beta oscillations synchronize across bilateral auditory cortices and motor-related areas, forming a functional sensorimotor network where beta oscillations play a key role (Haenschel et al., 2000; Abbasi and Gross, 2020; Gourévitch et al., 2020). Even in passive auditory conditions, beta oscillations dynamically configure the sensorimotor network, reflecting functional coordination between auditory and motor systems (Fujioka et al., 2012, 2015). Auditory feedback has been shown to reduce alpha spectrum in the ipsilateral sensorimotor area and beta spectrum bilaterally, decreasing Beta-CMC while enhancing motor precision (Guo et al., 2022). Similarly, optimal noise conditions improve motor accuracy and enhance motor spectral power (SP) and Beta-CMC (Trenado et al., 2014). These findings suggest that stochastic resonance enhances motor performance, consistent with increases in motor SP and CMC (Mendez-Balbuena et al., 2012; Trenado et al., 2014).

Beta-CMC is modulated by various external sensory signals. For instance, reduced visual feedback decreases the peak frequency of Beta-CMC and increases its amplitude, accompanied by a reduction in EEG Beta-band power (L'Abbate et al., 2022). Increased tactile feedback leads to right occipital cortex Beta-ERD and smaller motor errors (Lin et al., 2012). High visual gain conditions result in more pronounced Beta-band desynchronization, superior motor performance, and fewer motor errors, with enhanced connectivity between the parietal and motor cortices (Chung et al., 2017). Older adults show higher correlations between visual feedback and CMC (Watanabe et al., 2020).

Currently, few studies confirm that sensorimotor feedback alters Beta-CMC. Exploring CMC changes under various conditions using multimodal, multisensory stimuli may help to deepen our understanding of communication between the cerebral cortex and muscles during different motor processes, revealing the complexity of the motor system with its unique functional features.

5 The influencing factors of Beta band corticomuscular coherence

Research on Beta-CMC has significantly advanced our understanding, yet several key challenges remain in areas such as mechanistic insights, personalized interventions, long-term effects, and practical applications. Addressing these challenges requires leveraging advanced technologies, emphasizing individual differences, conducting long-term follow-up studies, and translating laboratory findings into clinical applications. By overcoming these challenges, we can deepen our understanding of CMC, develop new strategies for improving motor function and treating neurological disorders, and ultimately enhance

both scientific research and patient health outcomes. Below is a summary of potential influencing factors on Beta-CMC, with a brief overview provided in Figure 4.

5.1 Age-related changes in Beta-band CMC

Age significantly impacts the motor system, with changes in Beta-CMC reflecting developmental and aging processes. During childhood, motor development relies on the formation and integration of neuronal networks within the sensorimotor system (Müller et al., 1991; Paus et al., 1999).

- Infants and children: Ritterband-Rosenbaum et al. (2017) observed significant increases in CMC within the 20–40 Hz frequency band between 9–25 weeks in infants, suggesting a sensitive period for corticospinal connection development.
- Adolescents and adults: beta-CMC increases with age, particularly around 20 Hz between ages 8–12 (James et al., 2008). Adults (20–30 years) exhibit higher CMC strength than children (8–10 years), primarily due to increased descending connections (Beck et al., 2021).
- Elderly: in the elderly, CMC increases under cognitive task conditions, but Beta-CMC declines in frequency while increasing in amplitude. However, older adults show a decline in M1's beta activity and CMC frequency, with an increase in amplitude (Johnson and Shinohara, 2012; Kamp et al., 2013). Bayram's et al. (2015) study showed significantly weakened CMC at all tested force levels in older adults.

Further research is needed to understand these age-related variations, particularly in older adults, to improve interventions aimed at mitigating motor decline associated with aging (Roeder et al., 2020; Yokoyama et al., 2020).

5.2 Individual differences in Beta-band CMC

Beta-CMC exhibits significant individual variability. Ushiyama et al. (2011) found substantial differences in the strength of oscillatory coupling between the motor cortex and spinal motor neurons among individuals.

- Force variability: the maximum value of CMC (CMC-max) positively correlates with the coefficient of variation of muscle force (Force-CV) and the power spectral density of muscle force output (Force-PSD) in various frequency bands.
- Types of contractions: during different types of muscle contractions (isometric, concentric, and eccentric), CMC and spinal excitability exhibit various changes (Glories et al., 2021; Glories and Duclay, 2023). Spinal inhibitory mechanisms may regulate Beta-band CMC, acting as a neural "filter" by modulating motor neuron activity (Williams and Baker, 2009; Williams et al., 2010; Matsuya et al., 2017). Sensory feedback variability and gain modulation at low and high beta frequencies also contribute to individual differences in CMC (Baker and Baker, 2003; Khademi et al., 2018).

5.3 Motor skill learning and control

Learning can enhance both CMC and motor performance. Méndez-Balbuena et al. (2012) showed that participants with and without pre-intervention CMC exhibited increases in CMC and motor performance after learning.

- Visuomotor skills: Perez et al. (2006) found that learning visuomotor skills increases Beta-CMC between cortical-spinal transmission and spinal motor neurons.
- Rhythmic patterns: learning to produce rhythmic musical patterns enhances corticomuscular communication (Lapenta et al., 2022).
- Strength training: 3 weeks of maximal strength training significantly increased muscle strength and improved motor coordination, associated with a reduction in antagonist muscle activation and CMC (Elie et al., 2021).

Exploring the impact of different exercise modalities on Beta-CMC can deepen our understanding of how exercise influences brain function and motor control.

5.4 Training status

Physical training engages multiple biological mechanisms, leading to significant changes in CMC and muscle coordination. Training status, especially in elite athletic groups, involves influences beyond motor skill learning. These influences include various behavioral and demographic factors that contribute to neurobiological differences. For example, elite athletes often have enhanced proprioception, muscle memory, and refined motor control, which are products of both intensive training and genetic predispositions.

- Athletes: long-term trained athletes like ballet dancers and weightlifters exhibit suppressed oscillatory coupling between the sensorimotor cortex and spinal motor neurons (Ushiyama et al., 2010). Strength trainers have the highest CMC strength and frequency, particularly in antagonist muscles (Dal Maso et al., 2017; Hortobágyi et al., 2021).
- Sports injuries: ACL injuries cause continuous imbalances in leg muscle strength. Patients with ACL reconstruction show decreased quadriceps strength and stability compared to uninjured controls (Sherman et al., 2023).

Similarly, the process of rehabilitation and the restoration of motor function post-injury can be seen as a specialized training status. This rehabilitation involves not just regaining lost strength and coordination but also adapting the brain-muscle communication to compensate for altered or damaged neural pathways. For instance, anterior cruciate ligament (ACL) injuries cause continuous imbalances in leg muscle strength, and patients

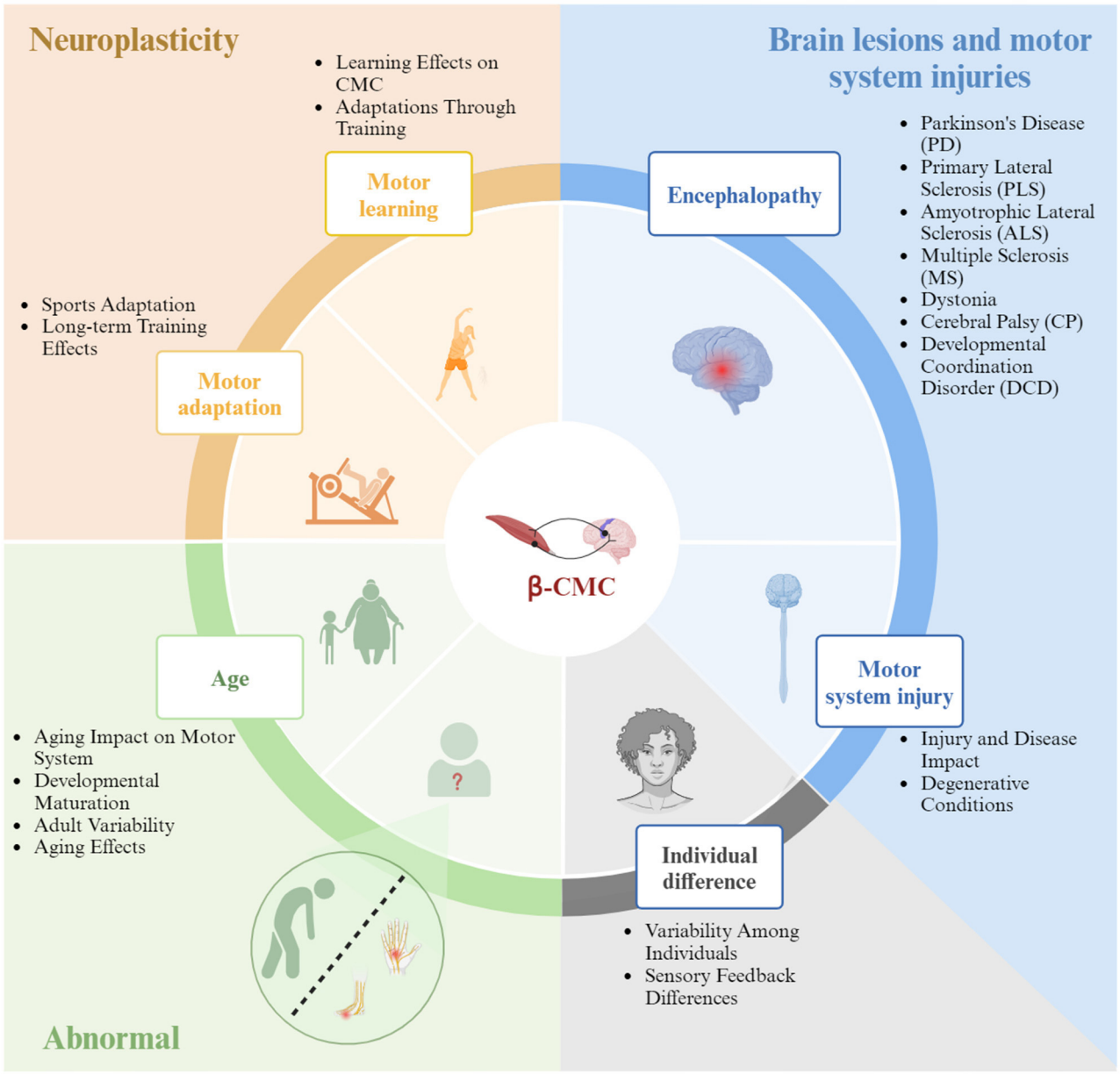

FIGURE 4
The influencing factors of Beta band corticomuscular coherence.

with ACL reconstruction show decreased quadriceps strength and stability compared to uninjured controls. Standardizing participant selection and exploring CMC indices during sport adaptation can provide insights into the dynamic relationships between the brain and muscles post-injury.

5.5 The abnormal state of the Beta band CMC

Pain and muscle fatigue impact CMC and motor performance.

- Pain: both noxious and non-noxious sensory inputs modulate the functional coupling between the motor cortex and muscles. Pain reduces CMC, increases EEG frequency, and decreases force stability (Burns et al., 2016; Poortvliet et al., 2019).
- Fatigue: muscle fatigue leads to reduced information flow in descending pathways and weakens Beta-band brain-muscle signal coupling (Tecchio et al., 2006; Yang et al., 2009). Increased cortical drive may help maintain motor performance in fatigue states but could also exacerbate central fatigue (Gandevia, 2001).

Future research should aim to optimize neuromuscular interactions to improve fatigue management and recovery strategies. This includes enhancing CMC during fatigue through targeted training programs, neuromodulation techniques, and

optimized recovery protocols. By focusing on the brain-muscle interplay under conditions of pain and fatigue, researchers can develop interventions to sustain motor performance and reduce injury risk, thereby enhancing athletic performance and well-being. Personalized approaches considering individual variability in pain perception and fatigue response can lead to more effective management strategies.

5.5.1 Neurodegenerative diseases related to the Beta band of CMC changes

Understanding corticomuscular interactions in various states is crucial for diagnosing movement disorders and developing effective treatments. Neurodegenerative diseases, characterized by neuronal loss and disrupted glial cell homeostasis, often feature altered beta oscillations.

- Parkinson's disease (PD): PD patients exhibit excessive beta activity in basal ganglia circuits and reduced cortical beta activity due to dopaminergic neuron loss in the substantia nigra. This imbalance leads to enhanced and synchronized beta oscillations linked to motor dysfunctions (McCarthy et al., 2011; Little and Brown, 2014; Cole et al., 2017). Reduced CMC in PD patients correlate with motor symptom severity (Zokaei et al., 2021). Beta-CMC changes serve as biomarkers for PD, with increased low-frequency (~10 Hz) and decreased ~30 Hz CMC during stable contractions (McKeown et al., 2006). Levodopa modulates abnormal Beta-CMC, indicating its potential as a pathological marker (Hirschmann et al., 2013).
- Primary lateral sclerosis (PLS) and amyotrophic lateral sclerosis (ALS): in patients with primary lateral sclerosis (PLS), significant Beta-CMC was detected in the ipsilateral primary motor cortex (M1). PLS primarily affects upper motor neurons, whereas amyotrophic lateral sclerosis (ALS) impacts both upper and lower motor neurons. PLS patients exhibit significant differences in CMC across various frequency bands, which extend beyond primary sensory-motor networks (Bista et al., 2023). ALS patients show reduced CMC and increased cortical-cortical coherence, highlighting cortical network impairments (Proudfoot et al., 2018).
- Multiple sclerosis (MS): MS patients exhibit motor system disorders and higher CMC frequency without significant amplitude differences, linked to functional connectivity changes (Tomasevic et al., 2013).
- Dystonia: characterized by sustained muscle contractions and abnormal movements, dystonia shows aberrant Beta-CMC modulation, suggesting distinct sensory-motor processing abnormalities (McClelland et al., 2020). Sensory tricks can improve sensory-motor integration in dystonia (Lee et al., 2021).
- Cerebral palsy (CP): CP patients exhibit higher Beta-CMC compared to healthy controls, unaffected by measurement time windows (Riquelme et al., 2014). Muscle fatigue impacts CMC similarly in CP and neurotypical adults, but CP patients show baseline deficiencies in cortical-muscle coherence (Forman et al., 2022).

Despite the significant potential of Beta-band cortico-muscular coherence (Beta-CMC) in diagnosing and assessing treatment efficacy for neurodegenerative diseases, current research faces several challenges and limitations. In Parkinson's disease (PD), patients exhibit a marked imbalance in beta oscillations; while Levodopa can modulate Beta-CMC, it does not address the progressive neuronal loss. The complexity of CMC changes in primary lateral sclerosis (PLS) and amyotrophic lateral sclerosis (ALS) is not fully understood, complicating treatment strategies. Multiple sclerosis (MS) patients show elevated CMC frequencies, but the underlying mechanisms of these functional connectivity changes remain unclear. In dystonia, abnormal Beta-CMC modulation indicates sensory-motor processing abnormalities that require further investigation. Cerebral palsy (CP) patients exhibit elevated Beta-CMC levels, yet the baseline deficits in cortico-muscular coherence warrant additional exploration. Most studies are constrained by small sample sizes and specific experimental conditions, limiting the generalizability of the findings. Future research should aim to validate these results in larger, more diverse populations and focus on long-term neuroplasticity and functional recovery mechanisms through longitudinal studies. Relying solely on Beta-CMC measurements may not fully capture the complex neurophysiological processes; integrating multiple biomarkers could provide a more comprehensive assessment. Moreover, the clinical application faces challenges such as device portability, ease of use, and real-time data analysis. Thus, developing user-friendly and reliable measurement and analysis tools is essential to advance the clinical utility of Beta-CMC.

5.5.2 Changes in Beta-band CMC resulting from motor system injuries

Motor system injuries, such as those from sports and strokes, significantly impact CMC and brain-muscle communication.

- Sports injuries: repetitive impacts, such as heading in soccer, can cause brain injuries. Studies show enhanced Beta-CMC in real environments but not in VR, possibly due to sensory input differences (Parr et al., 2023b). This compensatory mechanism may indicate a risk of long-term brain injury while demonstrating the brain's adaptive strategies (Campus et al., 2012; Chipaux et al., 2013). While such adaptations could indicate a risk of long-term brain injury, they also demonstrate the brain's strategy to cope with challenges.
- Stroke: stroke-induced motor impairments are linked to brain network reorganization. Stroke patients show widespread CMC peaks, including contralateral hemisphere peaks (Rossiter et al., 2013; Krauth et al., 2019). Changes in CMC correlate more with post-stroke duration than with motor recovery degree (von Carlowitz-Ghori et al., 2014). Motor performance improvement post-stroke is associated with increased Beta-CMC over time (Larsen et al., 2017). Another study reported that as motor ability gradually recovered post-stroke, Beta-CMC increased over time, surpassing levels seen in healthy controls (Krauth et al., 2019).
- Spinal cord injuries (SCI): SCI patients exhibit higher muscle co-activation and lower frequency CMC, particularly in

intermuscular coupling (Zu et al., 2023). Despite unchanged cortical efficacy, SCI patients increase muscle activation to compensate for reduced cortico-muscular communication (Cremoux et al., 2013).

In neurobiology, changes in beta-band cortico-muscular coherence (Beta-CMC) resulting from motor system injuries exhibit several commonalities. The brain demonstrates significant adaptive mechanisms to cope with injuries such as sports injuries, strokes, and spinal cord injuries, reorganizing brain-muscle communication pathways. For instance, enhanced Beta-CMC in real environments for sports injuries indicates adaptation to sensory inputs, while in stroke patients, Beta-CMC increases over time, reflecting cortical reorganization. Similarly, spinal cord injury patients compensate for reduced cortico-muscular communication by increasing muscle activation. Furthermore, Beta-CMC serves as a potential biomarker for recovery and adaptation. In stroke patients, Beta-CMC progressively increases with motor recovery, eventually surpassing healthy controls. Changes in Beta-CMC in sports and spinal cord injury patients also reflect their adaptive mechanisms, aiding in assessing rehabilitation progress and designing personalized strategies. These commonalities provide insights into the functional connectivity between the brain and muscles post-injury and highlight Beta-CMC's potential as a biomarker for guiding rehabilitation therapies.

Although beta-band cortico-muscular coherence (Beta-CMC) shows potential in assessing recovery following motor system injuries, several limitations remain. Current research predominantly involves small sample sizes and specific experimental conditions, which may limit the generalizability of findings. Future studies should aim to validate these results across larger and more diverse patient populations. Additionally, while existing studies primarily focus on short-term recovery, there is a significant gap in understanding the mechanisms underlying long-term neuroplasticity and functional recovery. Longitudinal studies are needed to address this gap. Moreover, Beta-CMC as a solitary biomarker may not adequately capture the multifaceted processes involved in motor function recovery. Integrating multiple biomarkers could provide a more comprehensive assessment. Furthermore, the clinical application of Beta-CMC faces practical challenges, including the portability of measurement devices, ease of operation, and real-time data analysis. To facilitate its clinical use, it is essential to develop user-friendly and reliable measurement and analysis tools. Therefore, despite its promise, future research should prioritize expanding sample sizes, investigating long-term effects, combining multiple biomarkers, and developing practical clinical tools to advance this field.

6 Beta band of CMC in clinical rehabilitation, and the application prospect in the field of competitive sports

Beta-CMC has significant potential to revolutionize clinical rehabilitation and enhance performance in competitive sports. Techniques like transcranial Direct Current Stimulation (tDCS), transcranial Alternating Current Stimulation (tACS), and Neuromuscular Electrical Stimulation (NMES) have shown promising results in enhancing CMC, thereby improving motor function and aiding in recovery from conditions such as stroke and multiple sclerosis (Bao et al., 2019; Padalino et al., 2021; Kudo et al., 2022). However, the effects of these techniques can vary significantly among individuals, indicating a need for personalized approaches (Schilberg et al., 2018; Ibáñez et al., 2023). Personalized approaches should consider factors such as individual neurophysiological profiles, optimal stimulation parameters, and the integration of multimodal feedback systems.

In competitive sports, understanding and optimizing Beta-CMC can provide critical insights into fatigue management, injury prevention, and skill refinement, leading to superior athletic performance. Future research should focus on the specific impacts of different exercise modalities and intensities on CMC (Pan et al., 2018; Xu et al., 2018; Koseki et al., 2021). Studies should also explore the interplay between CMC and various forms of athletic training to determine the most effective methods for enhancing performance. Advancements in non-invasive brain stimulation and neuroimaging techniques are expected to further our understanding of Beta-CMC mechanisms, facilitating personalized rehabilitation strategies tailored to individual neural dynamics. Interdisciplinary research is crucial to fully leverage the potential of Beta-CMC in both clinical and athletic contexts, refining current practices and developing innovative approaches for enhancing motor function and recovery. See Table 2 for a summary of changes in Beta-band CMC in clinical rehabilitation and competitive sports.

7 Future directions

This review underscores the integral role of Beta-CMC in advancing motor control. Future studies should explore individualized neuromodulation strategies, incorporating real-time neurofeedback to optimize CMC modulation based on personal neurophysiological profiles (Ding et al., 2023). By understanding the mechanistic basis of Beta-CMC across different motor tasks and its modulation via neuromodulation techniques, personalized medicine approaches can be developed to customize interventions according to individual cortical rhythms and motor profiles. Addressing the variability and dynamics of Beta-CMC through targeted research will enhance the efficacy of therapeutic interventions and athletic training programs.

7.1 Individual variability in CMC responses

Existing research indicates significant variability in the effectiveness of personalized approaches, which is likely attributable to differences in individual neurophysiological characteristics. However, the specific mechanisms underlying these differences remain unclear. Investigating these mechanisms is crucial for optimizing personalized treatment strategies and improving outcomes. Below are some rigorous examples that discuss the causes of individual differences:

1. Neuroanatomical differences:

TABLE 2 Changes in Beta-band CMC in clinical rehabilitation and competitive sports.

Application area	Findings and changes	References
Clinical rehabilitation		
tDCS and tACmS	Immediate enhancements in CMC and MEPs, particularly in stroke and MS patients, showing greater recovery effects	Bao et al., 2019; Padalino et al., 2021; Kudo et al., 2022
Individual differences	Effects of tACS on CMC vary among individuals; 20 Hz tACS modulates MEP amplitude in some studies but has unclear effects on Beta-CMC	Schilberg et al., 2018; Ibáñez et al., 2023
NMES	NMES at beta frequencies impacts CMC and voluntary motor output correlation; combined with exercise training shows significant rehabilitation effects.	Pan et al., 2018; Xu et al., 2018; Koseki et al., 2021
BCI and neurofeedback	Enhances Beta-CMC control, especially in chronic stroke patients; real-time CMC feedback training improves motor function.	von Carlowitz-Ghori et al., 2015; Belardinelli et al., 2017; Khan et al., 2020; Khademi et al., 2022
Competitive sports	Future direction	
Fatigue management	Optimizing CMC provides critical insights into fatigue management, injury prevention, and skill refinement	Søgaard et al., 2006; Yang, 2008; Yang et al., 2009; Tomasevic et al., 2013; Liang et al., 2021
Athletic performance	Specific impacts of different exercise modalities and intensities on CMC need further study	Dal Maso et al., 2012, 2017
Personalized training	Understanding and optimizing CMC can lead to superior athletic performance and training outcomes	Ushiyama et al., 2010; Elie et al., 2021

- Case study: Schilberg et al. (2018) found significant differences in the effects of tACS among individuals, potentially related to neuroanatomical variations. Some individuals exhibit stronger neuronal synchronization at specific frequencies, while others do not. These differences may stem from factors such as cortical thickness and gray matter density.

2 Neurophysiological state:

- Experimental study: Ibáñez et al. (2023) found that baseline neural activity levels significantly influence the effectiveness of tDCS. Individuals with higher baseline neural activity levels showed more pronounced improvements in CMC with the same stimulation intensity. This indicates that the neurophysiological state of an individual is a crucial factor affecting treatment outcomes.

3. Individualized neurofeedback systems:

- Empirical evidence: Koseki et al. (2021) demonstrated that sensory inputs based on individual CMC frequencies significantly affect the relationship between CMC and voluntary motor output. This suggests that personalized sensory feedback systems are essential for optimizing treatment outcomes.

4. Long-term adaptive changes:

- Longitudinal study: Xu et al. (2018) found that long-term exercise training combined with sensory stimulation significantly enhances CMC, with substantial individual differences. This indicates that athletes experience adaptive changes in their nervous systems over time, reflecting different adaptive mechanisms among individuals.

Investigating these individual differences will provide important references for optimizing personalized treatment strategies, thereby improving therapeutic outcomes and athletic performance.

8 Summary

Beta-band corticomuscular coherence holds significant potential in clinical rehabilitation and competitive sports. Future research should prioritize exploring individualized neuromodulation strategies, incorporating real-time neurofeedback to optimize CMC modulation based on personal neurophysiological profiles. By understanding the mechanistic basis of Beta-CMC across different motor tasks and its modulation through neuromodulation techniques, personalized medicine approaches can be developed to customize interventions according to individual cortical rhythms and motor profiles. This personalized approach could significantly improve therapeutic outcomes and athletic performance by addressing the unique needs of each individual.

Author contributions

JP: Writing – original draft, Writing – review & editing. TZ: Writing – original draft, Writing – review & editing. ZS: Investigation, Writing – original draft, Methodology. KS: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Neural oscillation in bipolar disorder: a systematic review of resting-state electroencephalography studies

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Bipolar disorder (BD) is a severe psychiatric disease with high rates of misdiagnosis and underdiagnosis, resulting in a significant disease burden on both individuals and society. Abnormal neural oscillations have garnered significant attention as potential neurobiological markers of BD. However, untangling the mechanisms that subserve these baseline alternations requires measurement of their electrophysiological underpinnings. This systematic review investigates consistent abnormal resting-state EEG power of BD and conducted an initial exploration into how methodological approaches might impact the study outcomes. This review was conducted in Pubmed-Medline and Web-of-Science in March 2024 to summarize the oscillation changes in resting-state EEG (rsEEG) of BD. We focusing on rsEEG to report spectral power in different frequency bands. We identified 10 studies, in which neural oscillations was compared with healthy individuals (HCs). We found that BD patients had abnormal oscillations in delta, theta, beta, and gamma bands, predominantly characterized by increased power, indicating potential widespread neural dysfunction, involving multiple neural networks and cognitive processes. However, the outcomes regarding alpha oscillation in BD were more heterogeneous, which is thought to be potentially influenced by the disease severity and the diversity of samples. Furthermore, we conducted an initial exploration into how demographic and methodological elements might impact the study outcomes, underlining the importance of implementing standardized data collection methods. Key aspects we took into account included gender, age, medication usage, medical history, the method of frequency band segmentation, and situation of eye open/eye close during the recordings. Therefore, in the face of abnormal multiple oscillations in BD, we need to adopt a comprehensive research approach, consider the multidimensional attributes

of the disease and the heterogeneity of samples, and pay attention to the standardized experimental design to improve the reliability and reproducibility of the research results.

KEYWORDS

Bipolar disorder, biological markers, neural oscillation, rsEEG, spectral power

1 Introduction

Bipolar disorder (BD) is a prevalent clinical mood disorder affecting approximately 1% of the global population (McIntyre et al., 2020), around 0.6% of the population in China (Huang et al., 2019). BD is characterized by early onset, frequent recurrence, high morbidity and mortality, with suicide risk being particularly prominent, posing a significant challenge to public health (Nierenberg et al., 2023; Dev et al., 2024). Due to atypical symptoms during the early stages of BD and the variability of symptoms, misdiagnosis and underdiagnosis are common, delaying effective treatment increasing the burden on patients and society (Craddock and Sklar, 2013; Bauer et al., 2018). Therefore, the quest for specific biomarkers to enhance the diagnostic accuracy of BD has become an urgent need in current research, as this will aid in early identification, timely intervention, and improved patient outcomes.

Neural oscillations have gained extensive attention as a potential biological marker of BD (Howells et al., 2018; Lu et al., 2022; Bokhan et al., 2023). Oscillations are defined as the repetitive and rhythmic electrical activity that occurs spontaneously or in response to stimuli within the central nervous system (Cole and Voytek, 2017; Han et al., 2021, 2023b; Wang et al., 2023). They play key roles in brain information processing, memory formation and emotion regulation (Fitzgerald and Watson, 2018; Cao et al., 2022; Han et al., 2022; Han et al., 2023a). Previous studies have found that bipolar disorder patients exhibit disturbances in neural oscillations, suggesting a dysfunction in brain network operations (Narayanan et al., 2015; Lu et al., 2022; Andrews et al., 2023). This dysfunction is not only manifested by altered oscillation intensity within specific frequency ranges but also by disrupted synchrony of oscillations between different brain regions. On a microscopic scale, the fine balance between excitatory and inhibitory neurons is considered one of the key pathophysiological mechanisms in BD (Schaul, 1998; Sohal and Rubenstein, 2019). When an E/I imbalance occurs, neuronal spiking becomes aberrant, leading to abnormalities in the brain's neural oscillation patterns.

Resting-state Electroencephalography (rsEEG) as a direct, non-invasive, and relatively inexpensive assessments measured the electrical field obtained from the summations at scalp electrodes of the oscillatory component generated by postsynaptic potentials in pyramidal cortical neurons (Biasiucci et al., 2019; Figure 1). The most common way to characterize rsEEG is by breaking down oscillatory signals into the spectral power of a frequency band (Figure 2). Power changes in specific frequency bands may be an indicator for an increased firing rate within certain cell populations reflecting different stages of cognitive arousal, cognitive processing, and psychopathology (Makeig et al., 2004).

Although there has been extensive recent research on the use of frequency bands in individuals with BD to investigate and understand changes in brain activity, there is no systematic review integrated the finding of BD and rsEEG. This is probably due to the heterogeneity of demographic and methodological elements. Therefore, the main purpose of our study was to find consistent abnormal resting-state oscillation patterns of BD thus providing a reliable foundation for improving early diagnosis and treatment strategies. Furthermore, we conducted an initial exploration into how methodological approaches might impact the study outcomes, underlining the importance of implementing standardized data collection methods.

2 Materials and methods

2.1 Search strategy and information source

We conducted a comprehensive search of English-language literature until March 2024 in PubMed and Web of Science, there was no limitation on publication date in search strategy. Following the Preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA) 2021 guidelines (Page et al., 2021). We focused on samples using terms "bipolar disorder". In terms of techniques, our interest encompassed "resting-state EEG," "quantitative EEG," "brain rhythms," and "brain oscillations." We used the Boolean expression "AND" to join the two terminologies. Moreover, the references of the selected articles were also examined to retrieve documents missed by the literature search.

2.2 Inclusion and exclusion criteria

The objectives of this paper and the inclusion criteria were structured based on the elements of the PICOS model (Population of interest, Interventions, Comparators, Outcomes, and Study design).

An article was included if rsEEG was assessed in a group of patients with BD. Only studies that investigated control group of health controls (HCs), either exclusively or in conjunction with other disease, were included in our review. The comparison of different states of BD was excluded. Studies employing alternative techniques, such as positron emission tomography (PET), magnetic resonance imaging (MRI), or magnetoencephalography (MEG),

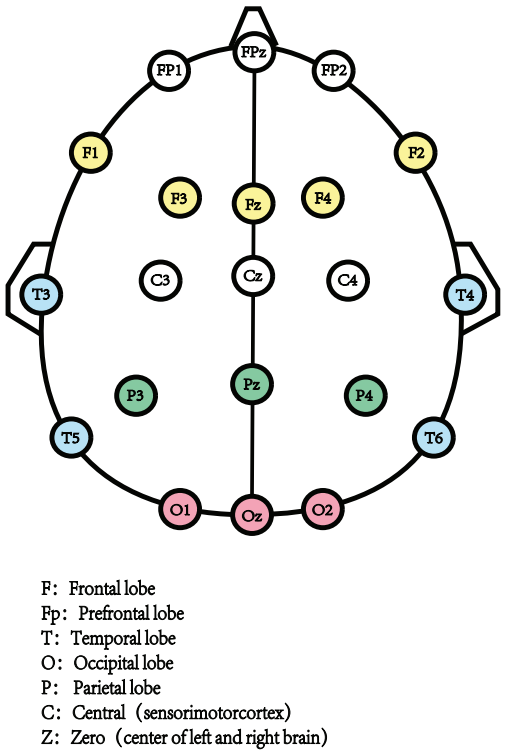

FIGURE 1
10–20 system EEG.

instead of EEG were excluded. We Use rsEEG to report spectral power in different frequency bands,studies exclusively focusing on other EEG metrics (e.g., asymmetry, coherence, functional connectivity, microstates, entropy etc.) were excluded. We only included empirical studies which written in English (Table 1).

2.3 Data extraction

Information from each included article was extracted and entered into tables, the extracted data included the following information: (1) authors and year of publication, (2) demographic characteristics (sample size, sex, age, disease and medication condition), (3) recording condition (eyes closed or eyes open), (4) measures of frequency bands and range (delta- δ, theta- θ, alpha- α, beta- β, gamma- γ), (5) spectral power type utilized, (6) main findings.

The selected articles and their data have been shown in the data extraction (Tables 3, 4). whereas the study outcomes were discussed in the results section. The analysis of the results has been generally explained in the discussion part.

2.4 Risk of bias assessment

The risk of bias in the included studies was assessed with a modified Newcastle Ottawa Scale. The case–control studies subscale was used for assessing the risk of bias. NOS provides three domains: (1) selection, (2) comparability and (3) exposure. The highest score is 9. A score from 9 to 7 indicates high quality, from 6 to 4 moderate quality, and from 3 to 0 low quality.

3 Results

3.1 Literature search and assessment of risk of bias

A total of 1096 articles were initially identified from Pub-Med and Web-of-Science databases using our search terms (Figure 3). 180 reviews, systematic reviews or meta-analyses were screened by automation tools, and 302 duplicate articles were removed. After reading the titles and abstracts, 586 articles were excluded. Upon further reading the full text, 18 articles were excluded, including 8 studies that did not address the outcomes of rsEEG spectral power changes. One study included only rsEEG frequency bands power ration (delta/alpha), instead of individual band power variations. Control group of 10 studies did not included HCs. Ultimately, 10 articles were included.

The mean score of quality assessment of the 10 studies was 5.6, indicating a moderate quality. Table 2 reports the score assigned to each article.

3.2 Character of the included studies

Table 3 show the demographic data and clinical characteristics of the 10 preferred studies. One articles only included women (Rommel et al., 2016), one article did not conclude sex information (Kano et al., 1992). Subjects of 2 studies were adolescents and young adults (El-Badri et al., 2001; Khaleghi et al., 2019). Two included articles control drug use (Başar et al., 2012; Khaleghi et al., 2019). In three studies, rsEEG was measured with eyes closed (Kano et al., 1992; Clementz et al., 1994; Arikan et al., 2019). However, three studies reported results for eyes open (Kam et al., 2013; Narayanan et al., 2015; Khaleghi et al., 2019), whereas four studies reported results for the eyes-closed and eyes-open conditions (El-Badri et al., 2001; Venables et al., 2009; Başar et al., 2012; Rommel et al., 2016).

Regarding frequency bands, of the 10 studies, 4 examined the conventional five frequency bands (delta, theta, alpha, beta, and gamma). Nevertheless, in 5 studies, the gamma band was excluded, 1 study only included alpha band (Başar et al., 2012). 4 studies split alpha or beta into sub-bands (e.g., alpha1/alpha2, beta1/beta2/beta3) (Kano et al., 1992; Clementz et al., 1994; Kam et al., 2013; Arikan et al., 2019). For each frequency band, power was mostly reported in terms of absolute spectral power, relative spectral power. For more details, see Table 4.

3.3 Reporting of frequency bands during resting state

3.3.1 Resting state delta spectral power

Table 4 shows the dominant results for frequency bands power for each study.

For Delta spectral power, 4 included studies indicated increased delta power compared to HCs (Clementz et al., 1994; El-Badri et al.,

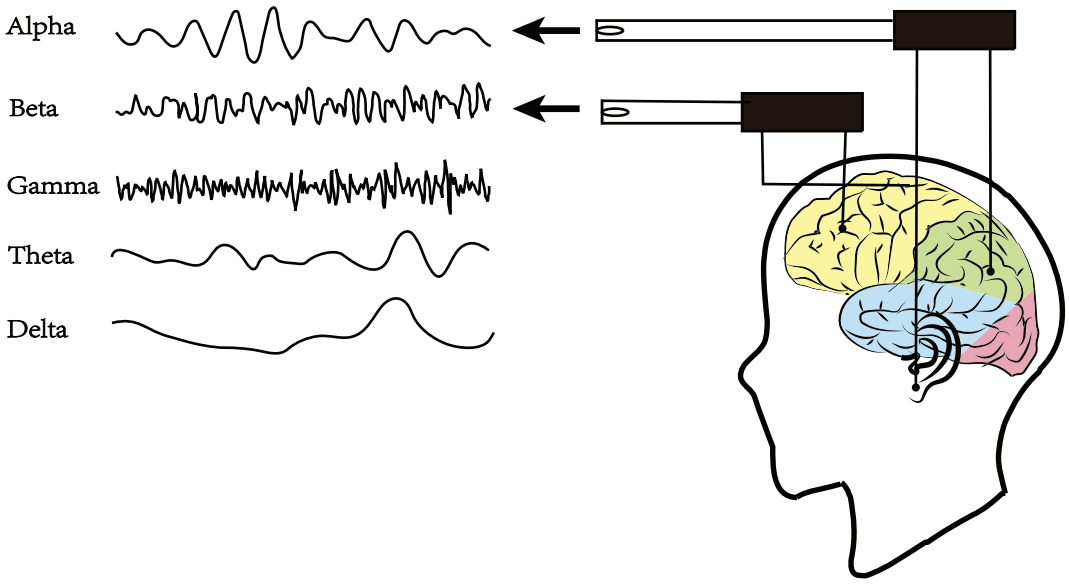

FIGURE 2
Frequency bands of brain oscillation.

2001; Narayanan et al., 2015; Khaleghi et al., 2019). Among them, Khaleghi drew the conclusion that delta frequency band of BD depression state exhibited great power in F7, F3, Fz, T3 (Khaleghi et al., 2019), and Clementz pointed out that the promote area was in C3, C4 and Cz (Clementz et al., 1994). The other 2 studies did not indicate the specific location of elevation. Three articles did not identify any statistical differences between BD and HCs patients (Venables et al., 2009; Kam et al., 2013; Rommel et al., 2016).

3.3.2 Resting state theta spectral power

A comparison of HCs, six studies showed an increase in resting-state theta power (Clementz et al., 1994; El-Badri et al., 2001; Narayanan et al., 2015; Arikan et al., 2019; Khaleghi et al., 2019; Kim et al., 2020). In term of the elevated brain areas, Khaleghi pointed out the findings in F3 and T3 (Khaleghi et al., 2019) and Arikan indicated that the greatest power activities are in FP1, P3, P4, Pz, O1, F7, T3 and T4 electrodes (Arikan et al., 2019). In 2020, Kim concluded that the resting state theta power increased at the global level, with the majority of this increase occurring in the frontal lobe (Kim et al., 2020). Two studies did not report any changes in the groups in the theta frequency band (Venables et al., 2009; Kam et al., 2013).

3.3.3 Resting state alpha spectral power

The outcomes regarding alpha oscillation in BD were more heterogeneous, In comparison with HCs, 4 studies showed alpha band power increased (El-Badri et al., 2001; Narayanan et al., 2015; Arikan et al., 2019; Khaleghi et al., 2019), while 4 articles indicated decreased alpha activities (Kano et al., 1992; Clementz et al., 1994; Başar et al., 2012; Kam et al., 2013). In 1992 Kano firstly proposed that alpha power was decreased in F7 (Kano et al., 1992), then Clementz suggested BD C3, C4, Cz has lesser alpha activities than HCs (Clementz et al., 1994). In 2012, Basar concluded decreased alpha power in O1, Oz, O2 (Başar et al., 2012).

TABLE 1 Inclusion and exclusion criteria of studies.

Inclusion criteria	Exclusion criteria
At least one group with BD	Experimental studies that lacked a comparison group of HCs
Studies use EEG to learn	Studies employing PET, MRI or MEG
spectral power in different frequency bands	Studies exclusively focusing on other EEG metrics (e.g., asymmetry, coherence, functional connectivity, microstates, entropy etc.)
Empirical studies	Reviews, commentaries, or meta-analysis
Written in English	Written in other languages

3.3.4 Resting state beta spectral power

In the comparison of BD to HCs, 5 studies showed an increase in beta band power (El-Badri et al., 2001; Kam et al., 2013; Narayanan et al., 2015; Arikan et al., 2019; Khaleghi et al., 2019). One study suggested that beta has greater power than HC in right temporal and left occipital particularly (El-Badri et al., 2001). Another study concluded: Beta power increased in FP1, FP2, C4, P3, O1 and F7. Beta 1 power increased in O1, and F7; Beta 2 power increased in O1 and F7; Beta 3 power increased in P3, O1 and F7 (Arikan et al., 2019).

3.3.5 Resting state gamma spectral power

In comparison between BD and HCs, 3 articles indicated increased gamma power (Kam et al., 2013; Arikan et al., 2019; Khaleghi et al., 2019). One included study indicated that gamma power increased in Fp1, F8, C3, T5, T6 and O1 (Khaleghi et al., 2019), another concluded that gamma power increased in C3, F7, with gamma 1 in C3, P3, F7, gamma 2 in Cz, P3, F7 and high gamma in C3, C4, F7 (Arikan et al., 2019).

TABLE 2 Quality Assessment of Documents (NOS Scale Case–Control Studies).

study	Selection (Maximum 4 stars)	Comparability (Maximum 2 stars)	Exposure (Maximum 3 stars)
Başar et al., 2012	***	*	***
Khaleghi et al., 2019	**	**	***
Rommel et al., 2016	**		***
Narayanan et al., 2015	**		***
Clementz et al., 1994	***	*	***
El-Badri et al., 2001	***		***
Arikan et al., 2019	**		***
Kano et al., 1992	*		***
Venables et al., 2009	***		***
Kam et al., 2013	*		***

*Represents one score.

4 Discussion

In this systematic review, our aim was to find consistent abnormal resting-state oscillation patterns of BD. Furthermore, we try to analyze the causes and mechanisms of discrepancies based on the results, while correlating them with the summarized demographic characteristics and experimental methods. We found that BD patients had abnormal oscillations in delta, theta, beta, and gamma bands, predominantly characterized by increased power, indicating potential widespread neural dysfunction, involving multiple neural networks and cognitive processes. However, the outcomes regarding alpha oscillation in BD were more heterogeneous, which is thought to be potentially influenced by the disease severity and the diversity of samples.

4.1 Delta oscillation

All these studies indicated an increase in the power of the delta frequency band in the studies included in this analysis, BD was compared with HCs. Delta oscillations may reflect homeostatic and metabolic processes. The predominance of low-frequency waves in consciousness is considered a pathological state, which is often associated with cognitive decline (Uhlhaas et al., 2008).

4.2 Theta oscillation

All of the included studies showed an increased frequency of theta waves in BD compared with HCs, and most of them indicated that they were located in the frontal region. Theta oscillations have been shown to index cognitive performance particularly in decision-making, attention focusing and learning (Klimesch, 1999; Nokia et al., 2012). Theta oscillations depend on a balance between excitatory Glx and inhibitory GABA neurons, with alternating E/I interactions being essential for the generation and maintenance of low-frequency theta rhythms (Nigbur et al., 2011). Moreover, reduced GABA levels and increased Glx levels may exist in BD patients, thereby disrupting the rhythm balance of theta oscillations but current conclusions are not yet uniform (Chase and Phillips, 2016). Theta wave oscillations play a crucial role in synaptic plasticity regulating, spatial information processing, and memory encoding within the cortical-hippocampal circuit (Buzsáki, 2002). Abnormal discharging of hippocampal cells is a common feature among patients with psychiatric disorders, providing a reliable neurophysiological model for cognitive deficits (Olypher et al., 2006). Synaptic and neural plasticity are crucial processes for brain function and development, playing an important role in mental illness (Toro and Deakin, 2007; Narayanan et al., 2015). Neurogenesis in the hippocampus is related to synaptic plasticity, memory, and learning. Abnormal hippocampal neurogenesis is closely linked to depression and other psychiatric disorders (Kempermann et al., 2008).

4.3 Alpha oscillation

The results of alpha activity are different. The power of alpha band is believed to be negatively correlated with cortical activity, concentration, and thalamus metabolism (Nusslock et al., 2012). The thalamus serves as the inlet for sensory transmission and plays a crucial role in concentration. The decrease in thalamus metabolism is correlated with an enhancement in alpha power (Lindgren et al., 1999). Therefore, it can be concluded that an increase in alpha activity is associated with attention deficits and thalamic metabolic disorder.

Moreover, increased alpha activity is associated with increased depression severity. BD patients with a high depression severity are characterized by decreased neuronal excitability. This abnormal neurophysiological pattern may affect the neurodevelopmental processes in adolescents with BD. Some researchers reported that the frequency bands of adolescents undergo changes. EEG is not as same as in adults during adolescent development (Khaleghi et al., 2019). Therefore, the different age groups of participants may be a potential reason for the controversy results. Moreover, some studies noticed that drug applications have effects on oscillation dynamics (Yener et al., 2007; Başar and Güntekin, 2008). Most of the studies we included did not control drug usage. The patient's treatment and medication may also have impact on the results which should be taken into account.

Another potential reason for the difference in the experimental results is the inconsistency of subjects included in the experiment. One study included 11 subjects with hypomanic and 10 subjects with depression (Khaleghi et al., 2019). Another study included subjects are all in an euthymic state (El-Badri et al., 2001). Khaleghi indicated BD I have greater delta power than BD II (Khaleghi et al., 2015). BD II is distinguished from BD I primarily by the absence of full-blown manic episodes. A growing body of evidence suggests that there could be neurobiological differences between

TABLE 3 Demographic and clinical characteristics.

Study	Subject	Sex	Age (years ± SD)	Medication	Recording
Başar et al., 2012	18BD (15BD I;3BD II) 18HC	13F; 5M 13F; 5M	31.66 ± 5.99 29.83 ± 7.77	euthymic 4w drug-free 2w	EO&EC
Khaleghi et al., 2019	21BD (11hypomanic;10depression) 18HC	11F;10M 9F; 9M	16.1 ± 1.51 16.3 ± 1.32	New onset drug-free	EO
Rommel et al., 2016	20BD I 20HC	All female	40.3 ± 7.7 36.7 ± 4.3	euthymic Uncontrolled	EO&EC
Narayanan et al., 2015	145 BP(psychotic) 56HC	60F; 85M 22F; 34M	37.07 ± 11.28 34.29 ± 12.05	uncontrolled	EO
Clementz et al., 1994	31BD 113HC	19F;12M 50F;63M	31 ± 14.2 22.5 ± 5.4	uncontrolled	EC
El-Badri et al., 2001	29BD I 26HC	10F;19M 14F;12M	30.7 ± 6.1 27.7 ± 7.0	Euthymic uncontrolled	EO&EC
Arikan et al., 2019	75BD 11HC	42F;33M 6F;5M	34.06 ± 11.12 33.80 ± 15.25	uncontrolled	EC
Kano et al., 1992	7BD 44HC	-	45.0 ± 17.0 41.5 ± 12.7	uncontrolled	EC
Venables et al., 2009	30BD 79HC	5F;25M 37F;42M	44.5 ± 9.5 43.7 ± 15.1	uncontrolled	EO&EC
Kam et al., 2013	76BD 136HC	40F; 36M 76F; 60M	41 39	uncontrolled	EO

F: female, M: male, EO: Eyes open; EC: Eyes close.

BD I and BD II patients, they presumed BD I has more deficits than BD II. These factors above may be the reason for the different results. Moreover, the EEG activity varies in different emotional states (Painold et al., 2014; Abé et al., 2016). The power of the alpha band was negatively correlated with the tension-calm (TC) score, that is, the power of the alpha exhibited higher power in the calm state than in the tension state (Wyczesany et al., 2010).

Significantly, some previous works have shown that alpha rhythms could be dissected into two components in scalp EEG, which might be related to different cognitive functions (Chiang et al., 2011; Knyazeva et al., 2018). Previous results have shown that the power in these different sub-bands (upper and lower alpha) also differed in resting state (Thorpe et al., 2016). Alpha power may be considered to inversely correlate with E/I balance, which display a negative correlation with cortical activation and metabolism (Conner et al., 2011; Podvalny et al., 2015). Thus, a signature of abnormally reduced alpha power would indicate a state of increased E/I, while the 'high-alpha' biotype would reflect low E/I (Bresnahan and Barry, 2002; Poil et al., 2014). In healthy subjects, alpha power increases or decreases have been found to reflect cortical inhibition or excitation, respectively (Haegens et al., 2011). This demonstrates the importance of clear band allocation.

Finally, it should be noted that during resting-state, some studies only recorded EO EEG (Kam et al., 2013; Narayanan et al., 2015; Khaleghi et al., 2019), while some studies only recorded EC EEG (Kano et al., 1992; Clementz et al., 1994; Arikan et al., 2019). According to some studies, the quantitative characteristics of the alpha rhythm can only be fully understood after one takes into account the spectral power and activation intensity (inhibition of the alpha rhythm after one opens their eyes, the Berger effect). One of the informative signs of the stability of the activation reaction is a decreased alpha power in response to the opening of the eyes (the Berger effect). This is associated with information processing (Kirschfeld, 2005).

4.4 Beta oscillation

High beta activity is associated with cortical excitability (Rangaswamy et al., 2002) and is generally considered to be facilitating (Moore et al., 2012). Some inferences can be drawn from literature reports indicating that an elevation of emotional tension is associated with an increased in beta power, particularly in the anterior region (Jacobs et al., 1996). Alpha activity is a fundamental rhythm in the brain. The increase in occipital beta power observed during manic episodes may serve as a compensatory mechanism for dysfunctional alpha responses (Wyczesany et al., 2010). Therefore, an increase in beta-band power may be accompanied by a decrease in alpha activity.

TABLE 4 Main quantitative EEG results.

Study	EEG variables	Delta	Theta	Alpha	Beta	Gamma
Başar et al., 2012	aSP	NA	NA	↓ (8–13Hz)	NA	NA
Khaleghi et al., 2019	aSP	↑ (0.5–4Hz)	↑ (4–8Hz)	↑ (8–13Hz)	↑ (13–34Hz)	↑ (34–45Hz)
Rommel et al., 2016	aSP rSP	NS (0.5–3.5Hz)	↑ (3.5–7.5Hz)	NS (7.5–12.5Hz)	NS (12.5–18.5Hz)	NA
Narayanan et al., 2015	Spatial weight	↑	↑	↑	↑	NS
Clementz et al., 1994	Mean of spectral power	↑ (1–3Hz)	↑ (3.125–8Hz)	↓ (8.125–13Hz)	NS Beta1 (13.125–20Hz) Beta2 (20.125–25Hz) Beta3 (25.125–30Hz)	NA
El-Badri et al., 2001	Mean of spectral power	↑ (0.5–3.9Hz)	↑ (4–7.9Hz)	↑ (8–14Hz)	↑ (14–22Hz)	NA
Arikan et al., 2019	aSP	↑ (1—4Hz)	↑ (4–7Hz)	↑ Alpha1 (8–10Hz) Alpha2 (10–12Hz)	↑ Beta1 (12–15Hz) Beta2 (15–18Hz) Beta3 (18–25Hz) High beta (25–30Hz)	↑ Gamma1 (30–35Hz) Gamma2 (35–40Hz) High gamma (40–50Hz)
Kano et al., 1992	significance probability mapping	NA	NA	↓ Alpha1 (8–9.5Hz) Alpha2 (10–12.5HZ)	NS Beta1 (13–19.5HZ) Beta2 (20–29.5Hz)	NA
Venables et al., 2009	aSP	NS	NS	NS	NS	NA
Kam et al., 2013	aSP	NS (0.5–4Hz)	NS (4–8Hz)	↓ Alpha1 (8–10Hz) Alpha 2 (10–12Hz)	↑ Beta1 (12–20Hz) Beta2 (20–30Hz)	↑ (30–50Hz)

aSP, absolute spectral power; rSP, relative spectral power; NS, not significant change; NA, not assessed.

4.5 Gamma oscillation

All studies reviewed herein consistently demonstrate an increase in gamma activities in individuals with BD compared to HCs. In addition, both BD and SCZ manifest overlapping symptoms, including psychotic symptoms, disorganized thinking, and depressive symptoms (Calhoun et al., 2011; Bora and Pantelis, 2016). Researches indicate that patients diagnosed with BD and SCZ exhibit notable abnormalities in neural processes involving gamma oscillations, which are both characterized by increased gamma activities (Zhou et al., 2018; Honda et al., 2020). The occurrence of gamma oscillation is contingent upon synaptic GABA neurotransmission, which is crucial for coordinating neural network activities across different brain regions (Lu et al., 2022). Cortical gamma activity plays a crucial role in processes such as sensory perception, problem-solving, and memory. Moreover, in BD the overexpression of the neuronal calcium sensor (NCS-1) protein modulates gamma band oscillation in the pedunculopontine nucleus (PPN) in a concentration-dependent manner (Urbano et al., 2014). Consequently, it can be inferred that the increased expression of NCS-1 leads to greater gamma band activity in BD patients.

Cortical gamma oscillations are believed to be generated independently of external stimuli, facilitated by GABA interneurons engaged in mutual inhibition. These interneurons generate postsynaptic potentials that oscillate at approximately 40 Hz. Consequently, gamma oscillations are considered oscillations are considered indicative of the inhibition of cortical neurons.

5 Critical considerations in EEG band analysis for BD research

Although the articles included in this review present promising findings, it is essential to acknowledge certain limitations identified in the analysis of frequency bands carried out in each of the reviewed investigations. Addressing these limitations is crucial for the progression of EEG research and its effective application in the study of BD.

Firstly, some researchers indicated that there are significant gender differences in EEG power between genders, with females exhibiting higher power than males (Narayanan et al., 2014). Moreover,several studies indicated that blood glutamate levels of females vary across the menstrual cycle and are negatively associated with the levels of female sex hormones (Tseng et al., 2024). It is therefore possible that males and females have different states of E/I balance. The changes may have effects on band

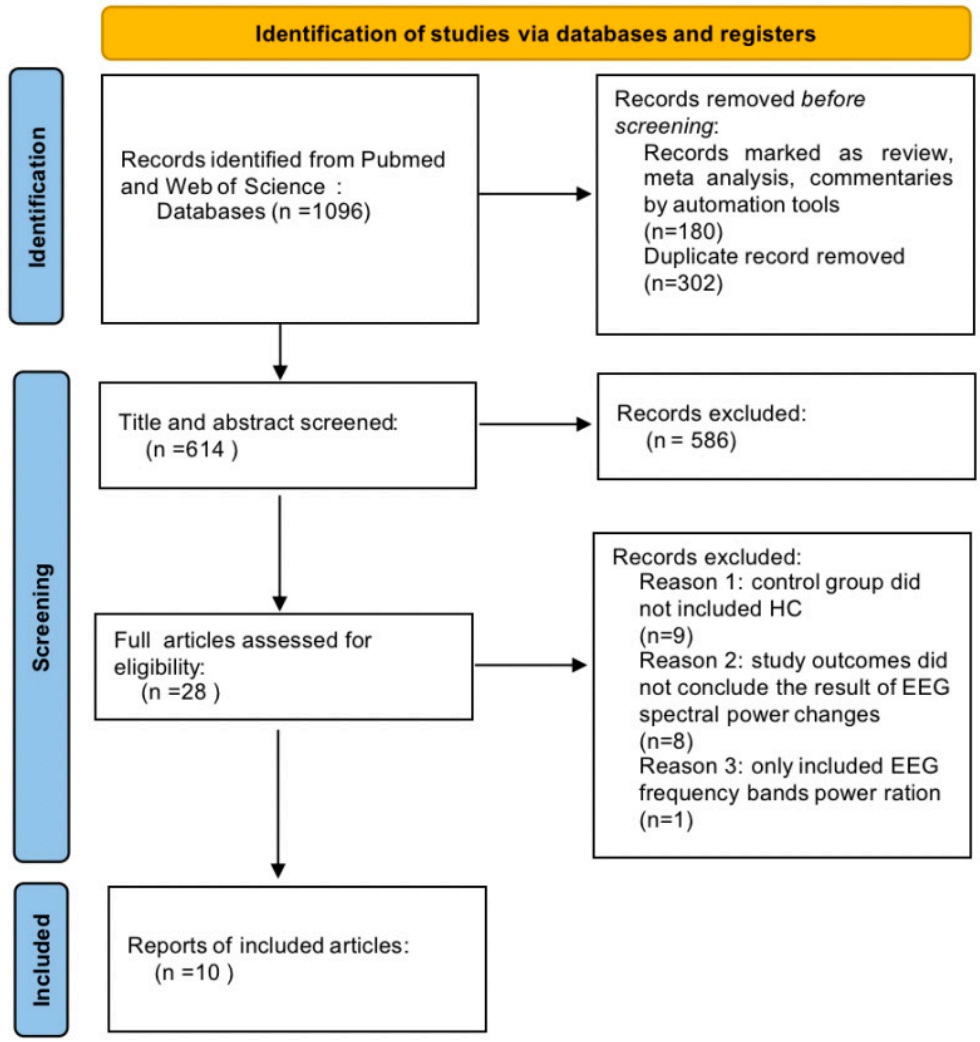

FIGURE 3
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection.

oscillation. This suggests that inconsistencies in the sex ratio of male and female in studies may have an impact on the results. While most studies showed that the results were not due to variable gender composition across groups. Although (Rommel et al., 2016; Bokhan et al., 2023) included only female, their outcomes limit the generalizability of findings in the BD patients.

Second, different experiments have defined the age range of patients differently (e.g., 12 to 18 years considered as adolescents (Khaleghi et al., 2019), and 18 to 40 years considered as young patients (El-Badri et al., 2001). A cross-sectional study on adolescents with BD indicated that the neural defects of BD may differ between adolescents and adults (Wegbreit et al., 2014). It remains unclear whether the pathology and mechanism of BD adolescents differ from those in adults. Additionally, epidemiological research suggests that there are multiple critical periods for the onset of BD, specifically in late adolescence, around the age of 20, and between 30 to 40 years (Bellivier et al., 2003). Therefore, it is imperative for further experimental designs to consider the range of age groups. 2 experiments have defined the age range of patients differently (e.g., 12 to 18 years considered as adolescents (Khaleghi et al., 2019), and 18 to 40 years considered as young patients (El-Badri et al., 2001).

Third, although many of our preferred studies suggested there is no correlation between medication and frequency bands oscillations and did not control for patients' drug use, some scholars indicated that the EEG results can be affected by drugs in the resting-state (Spatz and Kugler, 1982; Struve, 1987; Schulz et al., 2000; de Meneses et al., 2022). For example, lithium usually increases slow wave activities (delta, theta) and decreases alpha activities. Some antidepressants (e.g., imipramine, viloxazine) may increase beta activities and simultaneously decrease alpha activities (Saletu, 1976; Bente, 1979). Amitriptyline tends to increase delta but decrease alpha activities (Peck et al., 1979). Studies on animal models have shown that mood stabilizers can exert behavioral effects by altering synaptic E/I balance (Tseng et al., 2024). Drugs used as mood stabilizers, including lithium, valproate and lamotrigine, have significant effects on the glutamatergic system (Sanacora et al., 2008).

6 Conclusion

Overall, the examined studies suggested that the electrophysiological features of BD probably could play a key role in diagnosis of this disease. In studying the characteristics of neural oscillations in BD patients, we observed abnormalities in multiple frequency bands such as delta, theta, beta, and gamma, the most notable feature of which was a general increase in oscillatory power. However, the results of studies of alpha oscillation show high heterogeneity, which may be due to the different stages and manifestations of symptoms of the disease, as well as the diversity of the samples themselves. Besides, we have preliminarily explored how the findings are influenced by demographic and methodological factors. By controlling for these variables, such as age, gender, stage of disease, comorbidities, and drugs used, researchers are better able to unravel the complexity of BD and reveal potential neurophysiological markers that inform future diagnostic and therapeutic strategies.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://pubmed.ncbi.nlm.nih.gov/?term=adult%20ADHD%20EEG&page=10.

Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Eye movement characteristics of emotional face recognizing task in patients with mild to moderate depression

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Objective: Depression is a complex affective disorder characterized by high prevalence and severe impact, commonly presenting with cognitive impairment. The objective diagnosis of depression lacks precise standards. This study investigates eye movement characteristics during emotional face recognition task (EFRT) in depressive patients to provide empirical support for objective diagnosis.

Methods: We recruited 43 patients with depression (Depressive patients, DP) from a psychiatric hospital and 44 healthy participants (Healthy Control, HC) online. All participants completed an EFRT comprising 120 trials. Each trial presented a gray screen for 800 ms followed by a stimulus image for judgment. Emotions were categorized as positive, neutral, or negative. Eye movement trajectories were recorded throughout the task. Latency of First Fixation (LFF), Latency of First Fixation for Eye AOI, and Latency of First Fixation for Mouth AOI were used as representative indicators of early attention, Proportion of Eye AOI, and Proportion of Mouth AOI as measures of intermediate attention, Accuracy (ACC) and Reaction Time (RT) as behavioral indicators of late-stage attention. In this study, these metrics were employed to explore the differences between patients with depression and healthy individuals.

Results: Compared to healthy participants, individuals with depression exhibit longer first fixation latencies on the eyes and mouth during the early attention stage of emotional face recognition, indicating an avoidance tendency toward key facial recognition cues. In the mid-to-late attention stages, depressive individuals show an increased fixation ratio on the eyes and a decreased fixation ratio on the mouth, along with lower accuracy and longer response times. These findings suggest that, relative to healthy individuals, individuals with depression have deficits in facial recognition.

Conclusion: This study identified distinct attention patterns and cognitive deficits in emotional face recognition among individuals with depression compared to healthy individuals, providing an attention-based approach for exploring potential clinical diagnostic markers for depression.

KEYWORDS

eye movement, depression, AOI, emotional facial expression recognition, cognitive deficit

1 Introduction

Depression is a complex affective disorder with significant emotional, cognitive, and physical symptoms, characterized by persistent low mood, reduced activity, and slowed cognitive function. According to the Global Burden of Disease Study, approximately 280 million people worldwide suffer from depression, including 5% of adults and 5.7% of individuals over 60, and 25% increase has been triggered by COVID-19 (World Health Organization, 2022). Depression is significantly associated with disability and can lead to severe consequences, including suicide, negatively impacting individuals' mental and physical health (Iancu et al., 2020; Morin et al., 2020).

Most patients with depression experience cognitive dysfunction, including deficits in executive function, attention, memory, and processing speed (Yan and Li, 2018). These impairments manifest as reduced cognitive flexibility, decision-making, and inhibitory control, along with difficulties in maintaining attention, short-term memory loss, and slower reaction times (Hollon et al., 2006; Koenig et al., 2014; Lee et al., 2012; Wagner et al., 2012). Depression also causes a negative emotional bias, where individuals exhibit a preference for negative stimuli, leading to the misinterpretation of information through a negative lens. This bias is linked to deeply ingrained negative self-schemas that sustain depressive symptoms (Jiang, 2024). Studies show depressed individuals have slower reaction times when recognizing facial expressions, particularly neutral ones, and reduced accuracy in identifying positive expressions, often mistaking them for neutral or negative (Leppanen et al., 2004; Sfarlea et al., 2018). However, they generally retain the ability to recognize sad expressions (Dalili et al., 2015).

The clinical diagnosis of depression primarily relies on patients' clinical symptoms supplemented by depression-related scale scores, lacking specific physiological and biochemical indicators as auxiliary diagnostic criteria (Cuijpers et al., 2020). This absence of a "gold standard" akin to the diagnosis of other organic diseases has prompted numerous studies in recent years to explore objective diagnostic indicators for depression using physiological signals, biochemical markers, and facial visual features (Byun et al., 2019; Koller-Schlaud et al., 2020; Rushia et al., 2020; Thoduparambil et al., 2020; Xing et al., 2019; Du et al., 2022).

The diagnostic approach based on facial visual features objectively assesses the severity of depression by analyzing relevant information from the patient's face. It further summarizes behavioral characteristics specific to individuals with depression to guide clinical diagnoses made by doctors. The equipment required for this method is simple—a camera—making it cost-effective and easily accessible. Importantly, subjects do not need direct contact with the equipment during data collection, allowing them to maintain a natural state of mind without any hindrance and ensuring genuine mental state data can be captured. Some scholars believe that this method is particularly beneficial for patients experiencing reduced interest or pleasure due to its user-friendly nature. Consequently, it holds significant research value and potential for development (Du et al., 2022).

Recently, there have been significant findings from eye movement experiments conducted on patients with depression. In free-viewing tasks, patients with depression show fewer fixation points and shorter total fixation times on positive images compared to healthy controls. Additionally, the transition time from negative to neutral stimuli was longer in the depression group than in the healthy group (Qian et al., 2019). In dot-probe tasks, it was observed that after undergoing positive word training, patients with depression showed a significant reduction in both the number and duration of fixations on the negative portion of pictures when compared to their pre-training performance (Liu et al., 2015). In recent years, an increasing number of researchers have integrated machine learning algorithms into modeling various indicators derived from eye movement experiments as well as other cross-modal indicators. The aim is to identify a combination method that yields optimal recognition rates for diagnosing depression (Pan et al., 2019; Shen et al., 2021; Wang et al., 2018).

Therefore, this study focuses specifically on individuals with mild to moderate depression and utilizes eye tracking technology to investigate different eye movement indicators during an emotional face recognition task among depressive patients. A comparison will be made against healthy individuals to enhance support for behavioral experimental data related to objective diagnostic indicators for depression while providing valuable reference data for future research involving emotional face recognition and eye movements among depressive patients.

2 Materials and methods

2.1 Participants

All participants were required to have normal or corrected normal vision, as well as be free from color blindness or color weakness to eliminate any potential impact of visual impairments on the experiment. Participants were aged between 18 and 60, right-handed, and were required to read the experimental instructions, agree to the procedures, and sign an informed consent form.

Depressed patients were recruited from a tertiary psychiatric hospital in Beijing. They were assessed by 2–3 psychiatrists, including one senior psychiatrist, using the 17-item Hamilton Depression Rating Scale (HAMD-17), and clinically diagnosed according to the criteria for depression outlined in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5). Patients scoring >7 on the HAMD-17 and clinically diagnosed with depression were included in the depression group, while individuals with other psychiatric disorders such as schizophrenia, anxiety disorders, or bipolar disorder were excluded.

The healthy control group was recruited online via social media platforms and consisted of volunteers. In addition to meeting the vision, age, and handedness requirements, healthy participants were required to score < 7 on the HAMD-17 and have a total score of <160 on the Symptom Checklist-90 (SCL-90).

A total of 45 participants were recruited for the depression group and 51 for the healthy control group. Due to data quality issues, 2 depressed participants and 7 healthy participants were excluded, resulting in a final sample of 87 participants, with 43 in the depression group and 44 in the healthy control group.

This study was approved by the Ethics Committee of the Institute of Clinical Basic Medicine, China Academy of Chinese Medical Sciences, under the approval number P23009/PJ09.

2.2 Experimental design and data collection

2.2.1 Emotional images

The emotional facial images used in the Emotional Face Recognition Task were sourced from the Chinese Affective Face

Picture System (CAFPS), developed by Professor Yuejia Luo's team at Shenzhen University (Xu et al., 2011). All images were standardized in terms of color, brightness, and size and demonstrated good reliability and validity. A total of 120 images were selected from the CAFPS database for the experiment, with 40 images for each emotional category (positive, neutral, negative). The images were matched for gender, with 20 male and 20 female faces in each emotional category.

2.2.2 Experimental instruments and software

The experiment employed a Tobii Pro X3-120 eye tracker produced by Tobii Technology AB, Sweden. The device is 324 mm in length, weighs 118 g, and operates at a sampling rate of 120 Hz. It can be directly mounted on monitors or laptops with screens up to 25 inches using the accompanying adhesive stand (as shown in Figure 1). During the experiment, participants were seated approximately 65 cm from the screen. Fixations were calculated using Tobii's built-in I-VT algorithm, which automatically identified fixations with a duration greater than 60 ms. Adjacent fixations separated by less than 75 ms and with an angular distance of less than 0.5 degrees were merged into a single fixation point. Eye-tracking data were collected and exported using Tobii Pro Lab Version 1.152. Behavioral data were collected, merged, and exported using E-Prime 3.0. Data preprocessing and statistical analysis were conducted using R Studio version 4.3.2, and data visualization was performed using GraphPad Prism version 10.1.2.

2.2.3 Experimental design and procedure

The experiment followed a 2 (group: depression patients/healthy controls) × 3 (emotional face type: positive/neutral/negative) mixed factorial design. Participants were required to complete the Emotional Face Recognition Task (EFRT), in which they were asked to identify the emotional attributes of randomly presented facial images. Meanwhile, the eye tracker recorded their eye movement trajectories.

Before the experiment, the eye-tracking equipment was calibrated. Upon arrival at the laboratory, participants were briefed on the task and informed of the relevant precautions. They then performed the Emotional Face Recognition Task. The experiment took place in a soundproof, windowless room, with the main light source being a ceiling light in the center. The computer faced the wall with its back to the light source to ensure soft, non-reflective lighting conditions.

The eye-tracking experiment followed an event-related design with a total of 120 trials presented in random order. The flow of a single trial is illustrated in Figure 1. Each trial began with a blank gray screen displayed for 800 ms, followed by the random presentation of an emotional face image at the center of the monitor. The duration of each image presentation was not fixed and depended on the participant's response. Participants were required to make a judgment by pressing one of three keys: "1" for positive, "2" for neutral, and "3" for negative. Once a selection was made, the trial ended, and the next trial began.

2.3 Data preprocessing and eye movement index calculations

2.3.1 Zoning and labeling of AOI

In Python, the shape key point coordinate prediction tool of the DLIB library and the standardized 68-point facial feature point calibration model are used to automatically identify the facial features coordinates of the stimulus images, the location is recorded by drawing and generating AOI coordinates table, and the AOI is judged

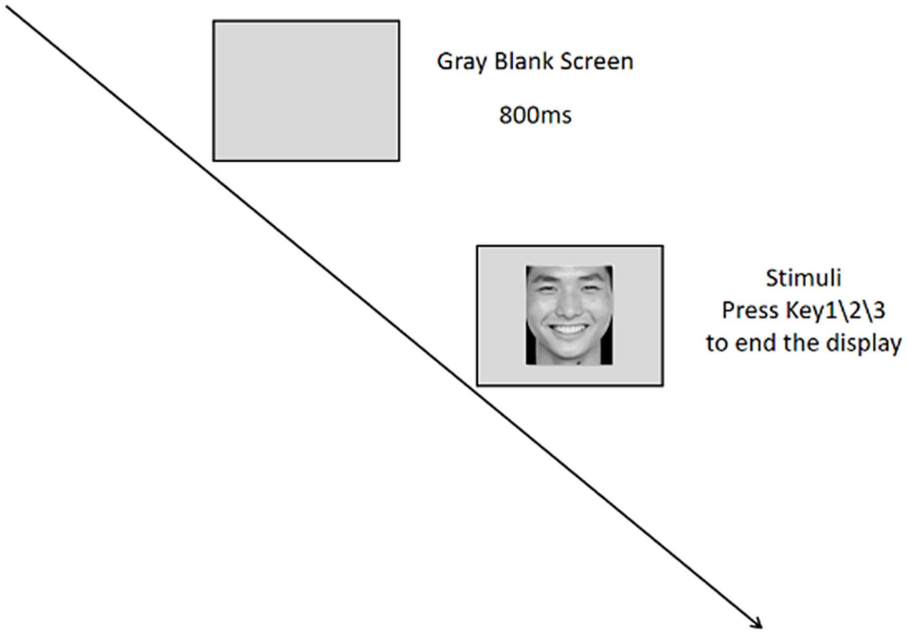

FIGURE 1
Processing diagram of the single trial.

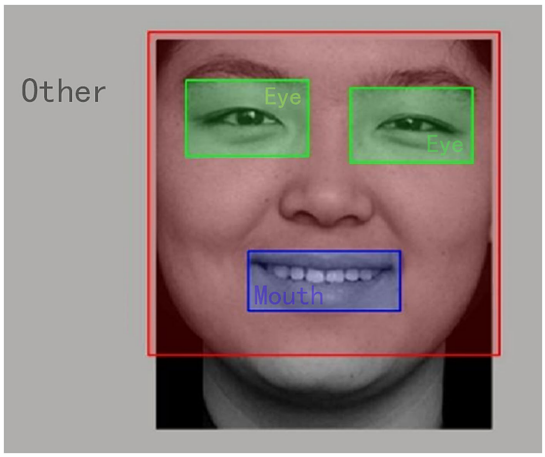

FIGURE 2
The effect diagram of AOI division.

by comparing the fixation point x and Y coordinates with the AOI coordinates, blue is Mouth, red is Face, and the Other areas are all Other (Figure 2).

2.3.2 Data screening and imputation

In this study, to clearly differentiate between eye-tracking data and reaction time/accuracy data, we referred to the latter as "behavioral data." Eye-tracking data were first stored in Tobii Pro Lab software, and during export, only data with a valid sampling rate of ≥60% were selected. Invalid sampling points during the experiment could result from undetected eye movements or unclassified samples, such as when participants blinked, closed their eyes, or looked away from the screen. During this process, data from two participants in the depression group were excluded.

Both eye-tracking and behavioral data were preprocessed and analyzed using R. Outliers beyond 1.5 times the interquartile range (IQR) were excluded. Missing values were imputed using mean substitution. After data cleaning, missing values were imputed as follows: Latency of first fixation (12%), LFF of eye (3%), LFF of mouth (3%), Look proportion of eye (2%), Look proportion of mouth (0%), Accuracy (9%), and Reaction time (5%).

2.4 Data analysis

In this study, the analyzed data primarily comprised eye-tracking and behavioral data. Eye-tracking metrics were derived from the raw data, including the latency of the first fixation (LFF) for each trial, the LFF of the eye AOI (area of interest), the LFF of the mouth AOI, the proportion of fixation time on the eye AOI, and the proportion of fixation time on the mouth AOI. Behavioral data included reaction time and accuracy.

2.4.1 Eye-tracking metrics calculation

First, the timestamps from the raw data were used to record the stimulus start time, end time, and the start and end times of each fixation point. Statistical metrics were then calculated using the following formulas.

2.4.1.1 Latency of first fixation

LFF-related eye-tracking metrics reflect early visual attention characteristics. By analyzing the LFF in different AOIs, early attention preferences can be inferred.

2.4.1.1.1 LFF for each trial

Calculated as the time from the stimulus onset (STS, Start Time of Stimulus) to the first fixation onset (STFF, Start Time of First Fixation). This measures the time from when the image appears until the first meaningful fixation occurs. Note that fixations that started before but ended after stimulus onset were excluded to ensure that the first fixation was drawn by the stimulus image.

2.4.1.1.2 LFF for eye AOI

Time from the stimulus onset to the first fixation on the eye AOI.

2.4.1.1.3 LFF for mouth AOI

Time from the stimulus onset to the first fixation on the mouth AOI.

2.4.1.2 Proportion of look time

Fixation proportion is calculated by measuring the fixation time in different AOIs. Fixation duration is a common metric for mid-term fixation analysis, but since the stimulus presentation time was not fixed in this study, fixation duration is highly correlated with reaction time, making it less suitable as a statistical metric. Instead, we converted fixation duration to a proportion, allowing a comparison of depression characteristics across different AOIs.

2.4.1.2.1 Look proportion of eye

First, the fixation duration for each AOI in a single trial was calculated, then summed to get the total fixation duration (total look time). The fixation proportion for each AOI was then calculated by dividing the fixation duration for that AOI by the total fixation duration. Look proportion of eye = Look time of eye AOI/Total look time

2.4.1.2.2 Look proportion of mouth

Similar to the above, Look proportion of mouth = Look time of mouth AOI/Total look time.

2.4.2 Statistical analysis

For demographic data, age differences between the two groups were analyzed using a *t*-test, and gender differences were compared using a chi-square test. Since age differences were significant, age was controlled as a covariate in the analysis of eye-tracking and behavioral data, using a 2×3 ANCOVA design. *Post-hoc* tests and simple effects analyses were corrected using the Bonferroni method for *p*-values.

3 Results

3.1 Demographic information

Demographic information was statistically presented in Table 1, there was no difference in gender composition between the DP group and the HC group, however, the age of the DP group was significantly larger than that of the HC group, so the covariance analysis was used to count the dependent variable and the age was a covariate to control for the subsequent statistics.

3.2 Analysis of covariance for statistical indicators

Table 2 showed the descriptive statistical table of the values of each dependent variable in the DP group and the HC group under different emotional face conditions, and the summary table of the results of analysis of covariance for all dependent variables was shown in Table 3.

The main effect of GROUP was not significant in the 2 × 3 ANCOVA with the LFF as the dependent variable, but it was significant in the ANCOVA with the LFF of Eye AOI [$F(1, 85) = 17.519$, $p < 0.001$, $\eta^2p = 0.016$] and LFF of Mouth AOI [$F(1, 85) = 21.329$, $p < 0.001$, $\eta^2p = 0.027$]. The first fixation latency of Eye AOI and Mouth AOI in DP group was significantly longer than HC group.

In the ANCOVA analysis of look proportion, the main effects of GROUP were significant both in Eye AOI [$F(1, 85) = 4.819$, $p = 0.029$, $\eta^2p = 0.048$] and Mouth AOI [$F(1, 85) = 11.791$, $p = 0.001$, $\eta^2p = 0.033$], the post-hoc test showed that the proportion of Mouth AOI in DP group is significantly lower than HC group.

The main effect of GROUP was also significant in the analysis of Accuracy [$F(1, 85) = 27.654$, $p < 0.001$, $\eta^2p = 0.036$] and Reaction Time [$F(1, 85) = 49.430$, $p < 0.001$, $\eta^2p = 0.060$], the *post-hoc* test showed that the accuracy of EFRT in DP group was significantly lower than HC group, and the reaction time in DP group was significantly longer than HC group.

4 Discussion

4.1 Avoidance of recognition cues in early attention

We found some interesting results on the latency of first fixation. For the whole picture (Figure 3a), there was no difference between the DP group and the HC group, but there were some differences when the latency of the first fixation in the different regions of interest was analyzed, people with depression pay attention to the pictures at the same time as healthy people, but they pay attention to the features later than healthy people.

Previous studies have shown that most of the implementation of emotional face recognition is focused on the eyes and mouth (Eisenbarth and Alpers, 2011). The eye is a major cue for recognizing negative emotions (Franca et al., 2023; Grainger and Henry, 2020), the latency of the first fixation of the eye was greater in the DP Group than in the HC Group, suggesting that depressed patients are slower to notice the eye site when recognizing expressions, as can be seen from Figure 3b, especially when judging positive and negative faces, the latency of the first fixation point of "Eyes" was significantly greater than that of the healthy group, this suggests that people with depression have significantly more avoidance of the eye region when it comes to recognizing faces with distinct facial expressions than healthy people. This is consistent with findings from a study on the effects of depressive tendencies on eye gaze in social interactions. The study found that while depressive tendencies do not affect attention to others' faces as a whole, they do influence attention to others' eyes, suggesting an avoidance of the eye region among individuals with depressive tendencies (Suslow et al., 2024). Furthermore, a comparison within the depression group revealed that the first fixation latency on the eye region was significantly longer for positive emotional faces than for neutral images. This suggests a stronger avoidance of the eye region in response to positive emotional faces among individuals with depression. It may also be due to the role of the eyes as a primary cue for recognizing negative emotions, which could counterbalance avoidance tendencies in response to negative faces, thus making avoidance less prominent for positive faces. Similarly, the first fixation latency on the mouth was longer in the depression group than in the healthy control group, indicating a slower attention shift to the mouth region when identifying emotional faces compared to healthy individuals. As shown in Figure 3c, this delay is particularly evident in responses to neutral and negative expressions, which may be attributed to the mouth's role as a key indicator of positive emotional expressions (Grainger and Henry, 2020). When judging positive emotional faces, people typically fixate on the mouth first, which might explain why differences in first fixation latency on the mouth between the depression and control groups are less pronounced for positive faces but more noticeable in neutral and negative conditions (Figures 4, 5).

The relevant LFF indicators reveal that, in the early attention stage, individuals with depression do not show a significant difference in response to stimulus images compared to healthy controls. However, they exhibit a certain delay in focusing on effective facial expression

TABLE 1 Demographic information for DP and HC.

	Group		χ^2/T	*p*-value
	DP (*n* = 43)	HC (*n* = 44)		
Gender (M/F)	(6/20)	(3/14)	$\chi^2 = 0.851$	0.356
Age	39.6 ± 13.6	26.8 ± 2.62	T = 6.095	<0.001***

TABLE 2 Descriptive statistical analysis.

Types of facial emotions	Positive		Neutral		Negative	
Group	DP(*N* = 43)	HC(*N* = 44)	DP(*N* = 43)	HC(*N* = 44)	DP(*N* = 43)	HC(*N* = 44)
Latency of first fixation (s)	0.26 ± 0.08	0.24 ± 0.06	0.27 ± 0.08	0.25 ± 0.07	0.25 ± 0.07	0.24 ± 0.07
Latency of first fixation for eye AOI (s)	1.04 ± 0.43	0.81 ± 0.42	0.82 ± 0.37	0.71 ± 0.32	0.92 ± 0.42	0.71 ± 0.35
Latency of first fixation for mouth AOI (s)	1.26 ± 0.57	1.05 ± 0.46	1.73 ± 0.66	1.33 ± 0.55	1.48 ± 0.61	1.20 ± 0.56
Look proportion of eye AOI	0.31 ± 0.11	0.31 ± 0.11	0.38 ± 0.13	0.34 ± 0.12	0.34 ± 0.11	0.33 ± 0.11
Look proportion of mouth AOI	0.22 ± 0.07	0.24 ± 0.07	0.17 ± 0.06	0.20 ± 0.07	0.18 ± 0.07	0.22 ± 0.06
Accuracy	0.96 ± 0.06	0.97 ± 0.04	0.89 ± 0.07	0.93 ± 0.07	0.91 ± 0.08	0.96 ± 0.04
Reaction time(s)	1.30 ± 0.45	1.03 ± 0.31	1.49 ± 0.43	1.21 ± 0.36	1.44 ± 0.43	1.07 ± 0.27

TABLE 3 Covariance analysis table.

	Main effect of group			Main effect of type of emotional images			Main effect of age			Interaction effect of group and type of emotional images		
	$F(1,85)$	P	η^2p	$F(2,85)$	P	η^2p	$F(1,85)$	P	η^2p	$F(2,85)$	P	η^2p
Latency of first fixation	1.599	0.207	0.012	0.112	0.894	0.001	1.675	0.197	0.007	0.444	0.642	0.003
Latency of first fixation for eye AOI	17.519	0.000	0.016	2.411	0.092	0.019	6.920	0.009	0.027	0.105	0.901	0.001
Latency of first fixation for mouth AOI	21.329	0.000	0.027	11.261	0.000	0.081	4.687	0.031	0.018	1.607	0.203	0.012
Look proportion of eye AOI	4.819	0.029	0.048	4.029	0.019	0.031	10.075	0.002	0.038	1.373	0.255	0.011
Look proportion of mouth AOI	11.791	0.001	0.033	8.822	0.000	0.065	1.034	0.869	0.000	1.034	0.357	0.008
Accuracy	27.654	0.000	0.036	5.286	0.000	0.062	0.745	0.022	0.020	0.745	0.476	0.006
Reaction time	49.430	0.000	0.060	10.539	0.001	0.055	1.136	0.001	0.040	1.136	0.323	0.009

cues. This phenomenon reflects, to some extent, a slowing in attention direction and a reduction in efficiency for emotion recognition tasks among individuals with depression.

4.2 Altered processing patterns in mid-to-late attention stages and facial recognition deficits

The look proportion is derived from fixation duration, which reflects the difficulty participants experience in completing the task—the longer the duration, the greater the difficulty (Goller et al., 2019). Some discrepancies exist between prior studies and the findings of this study. Most studies suggest that individuals experiencing sadness tend to focus less on the eyes during facial recognition (Hills and Lewis, 2011), and individuals with depression engage in less eye contact during conversations (Fiquer et al., 2018). In social interactions, eye contact represents crucial information in the dialogue, conveying social interest and closeness (Cui et al., 2019). By diverting their gaze from others' eyes, individuals with depression may avoid deeper social engagement (Hames et al., 2013). The observed differences may be attributed to the specificity of this experimental task. Studies that use look proportion as a measure typically employ a free-viewing paradigm, where participants have ample time to view images. However, in this study, participants were required to respond to stimulus images as quickly as possible, with the images disappearing immediately after the response. Since facial expression recognition generally begins with the eyes and then moves to the mouth (Xue and Yantao, 2007), it is possible that limited viewing time in this study resulted in a focus advantage for the eyes as the first facial feature noticed. Given that both the depressed and healthy groups were under the same task conditions, a more plausible explanation may be an altered facial recognition pattern among individuals with depression.

In this study, Figures 3d,e reveal that individuals with depression show a higher look proportion on the eyes but a significantly lower look proportion on the mouth compared to the healthy control group. This suggests that during the task, participants in the depression group attempt to gather cues more from the eyes and less from the mouth. Research on facial expression recognition patterns in healthy individuals indicates a general preference to seek emotional cues from the mouth, with the eyes providing comparatively less prominent cues (Wang et al., 2011). Thus, these findings may suggest that individuals with depression have an altered facial expression recognition pattern compared to healthy individuals. When considering response time and accuracy, the accuracy rate in the depression group was lower than that in the healthy control group, while response times were longer. This indicates that individuals with depression are not only slower in recognizing emotional faces but also less accurate. These results imply that a facial emotion recognition pattern focused more heavily on the eyes is less effective for individuals with depression than for healthy individuals, highlighting deficits in emotional face recognition among those with depression compared to healthy controls.

5 Conclusion

Individuals with depression display certain disadvantages and deficits in attention characteristics during emotional face recognition tasks compared to healthy individuals. Specifically, depressive participants exhibit increased first fixation latency to key facial cue areas (eyes and mouth), indicating an avoidance of effective cues in facial recognition. They also show a decreased look proportion on the mouth and an increased look proportion on the eyes, accompanied by reduced accuracy and prolonged response times. These findings suggest changes in cognitive patterns and deficits in facial recognition during emotional processing in individuals with depression. The results of this study support the hypothesis that individuals with depression have cognitive impairments and facial recognition deficits, offering an attention-based approach to exploring clinical diagnostic markers for depression.

6 Limitations and future directions

In recruiting healthy controls and screening them using scales, the healthy participants' ages were relatively concentrated,

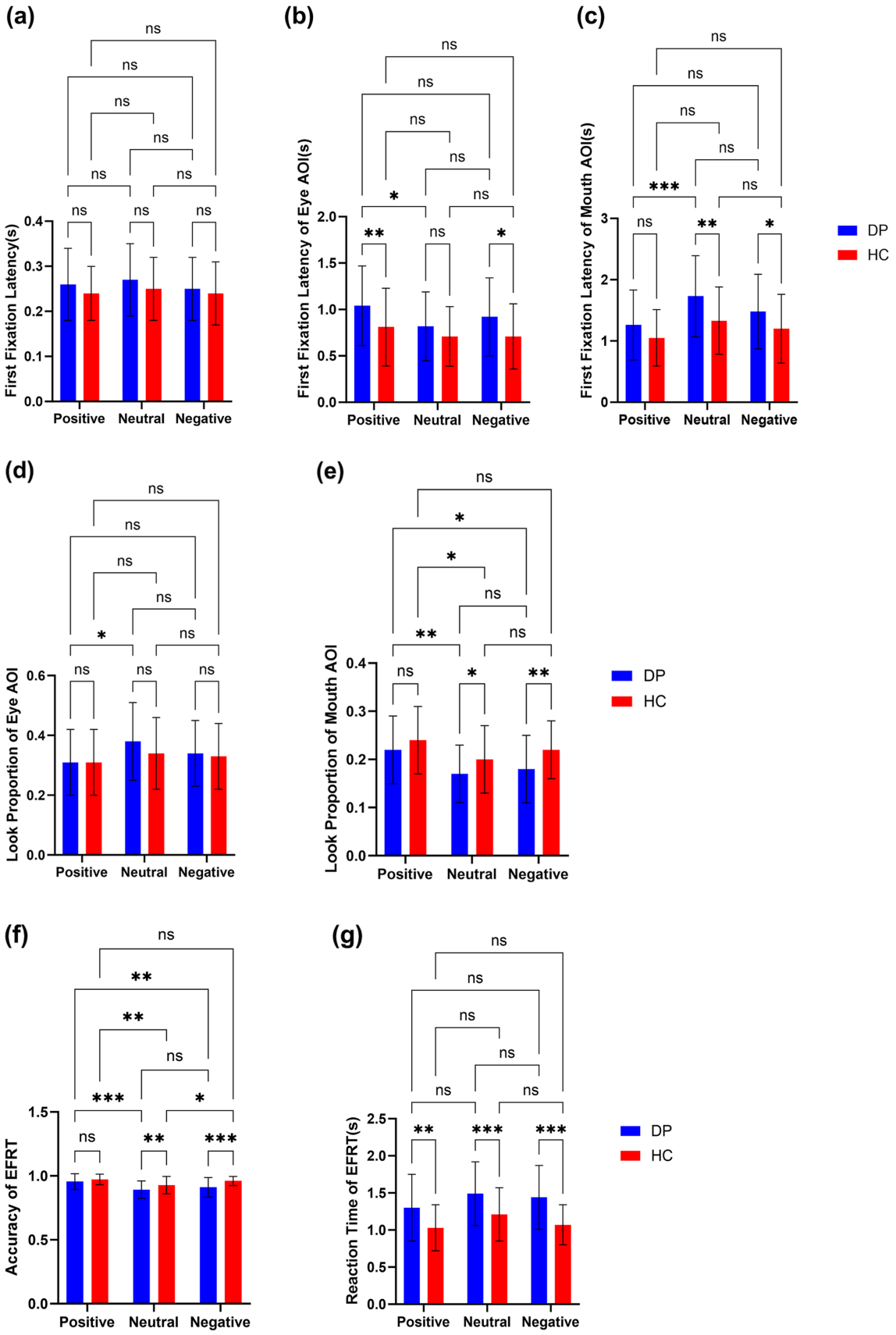

FIGURE 3
(a–c) Latency of first fixation in EFRT(s). (d,e) Look proportion of AOIs (eye and mouth) in EFRT. (f,g) Accuracy and reaction time(s) of EFRT. ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$; ns, non-significant.

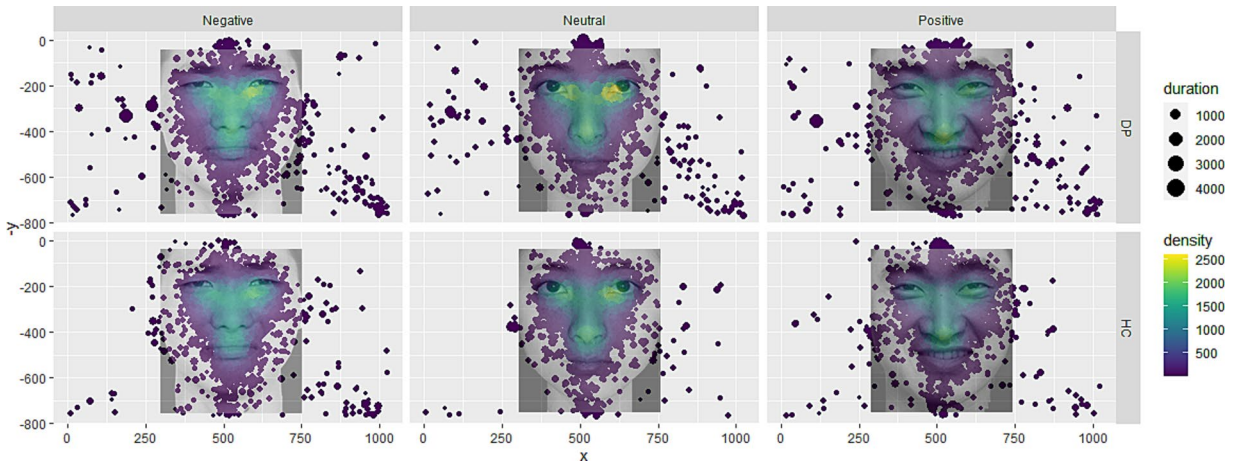

FIGURE 4
Fixation point heat map. Larger size of the fixation point represents longer fixation time, and the higher the color heat, the higher the density.

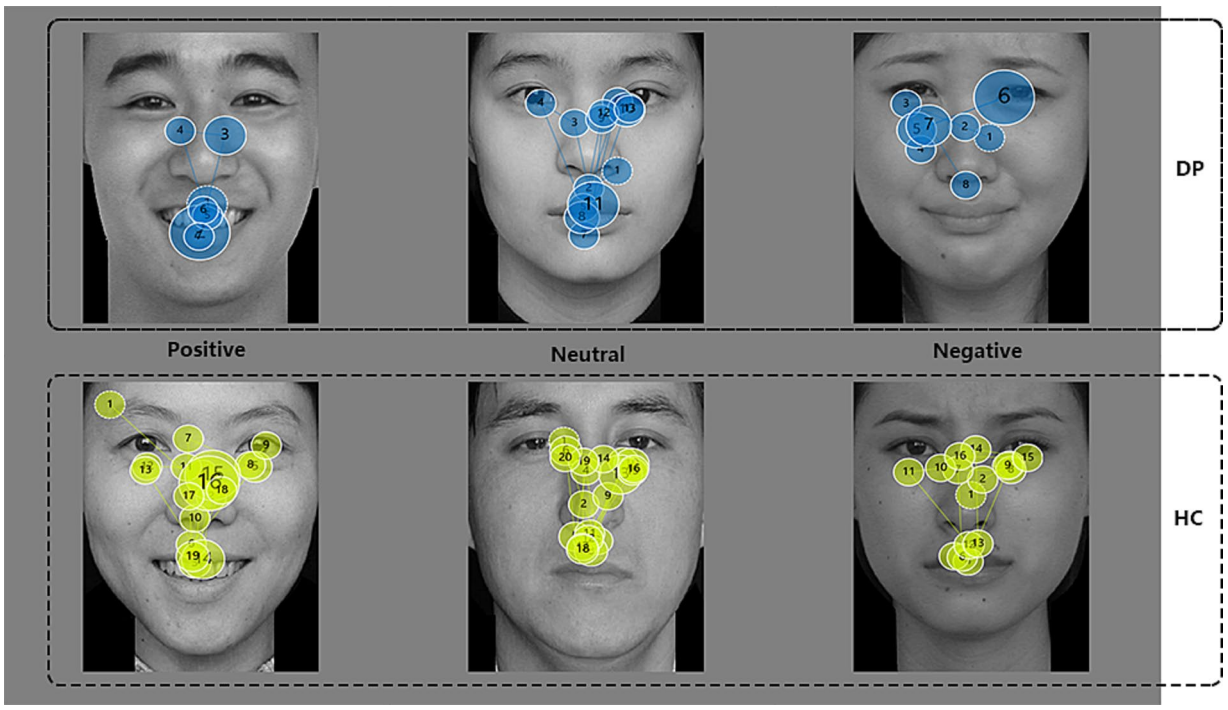

FIGURE 5
Eye trace images of DP and HC groups. The number in circle represents the order of fixation points, the size of the circle represents the duration of fixation, and the larger the circle, the longer the duration.

creating a disparity with the experimental group. Future research should increase the sample size to match the ages of the healthy control group more closely with the experimental group. What is more important is that the conclusions of this study need further validation in future research.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the Institute of Clinical Basic Medicine, China Academy of Chinese Medical Sciences. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

QiaY: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. YF: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. QiuY: Conceptualization, Funding acquisition, Resources, Supervision, Writing – review & editing. DY: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing. YZ: Conceptualization, Resources, Supervision, Writing – review & editing. HW: Funding acquisition, Supervision, Writing – review & editing. HZ: Investigation, Writing – review & editing, Validation. YS: Investigation, Writing – review & editing. XX: Investigation, Writing – review & editing. JD: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer XS declared a shared affiliation with the author YS to the handling editor at the time of review.

Publisher's note

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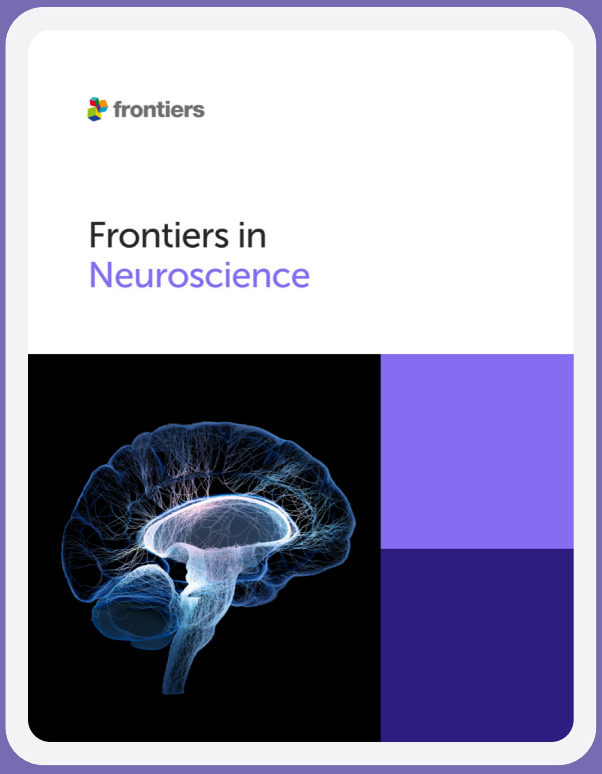

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